UNITED STATES FOOD AND DRUG ADMINISTRATION

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PEDIATRIC ADVISORY COMMITTEE MEETING

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Monday-Tuesday, May 7, 2012

Hilton Rockville Executive Meeting Center

1750 Rockville Pike

Rockville, Maryland, 20852

The meeting was convened at 8:00 a.m.,

GEOFFREY ROSENTHAL, M.D., Ph.D., Chairman, presiding.

MEMBERS PRESENT:

GEOFFREY ROSENTHAL, M.D., PH.D., CHAIRMAN, PRESIDING

#BRAHM GOLDSTEIN, M.D.

KATHLEEN MOTIL, M.D., PH.D.

ALEXANDER RAKOWSKY, M.D.

KENNETH TOWBIN, M.D.

JEFFREY KRISCHER, PH.D.

VICTOR SANTANA, M.D.

JEFFREY WAGENER, M.D.

MICHAEL D. REED, PHARM.D, F.C.C.P., F.C.P.

CONSULTANTS

† AMY CELENTO, B.S.

GERI D. HEWITT, M.D.

CHARLES M. GLASIER MD

*MARK HUDAK, M.D.

MICHAEL WHITE, M.D., PH.D.

PHILIP LARUSSA, M.D.

JONATHAN MINK, M.D., PH.D.

SHARON RAIMER, M.D.

JESSE JOAD, M.D., M.S.

∞BRIDGETTE WIEFLING, M.D.

ALSO PRESENT: WALTER ELLENBERG, Ph.D.,

Executive Director and Designated Federal Official

* Acting Healthcare Representative
# Industry Representative
† Acting Patient-Family Representative
∞ Acting Consumer Representative

P R O C E E D I N G S

(8:03 a.m.)

WELCOME AND INTRODUCTORY REMARKS

CHAIRMAN ROSENTHAL: Hi, well, let's keep going. It's been kind of a crazy morning. I know traffic has been bad, so it's been hard for people to get in. And, for those of you who are staying at the hotel, and were expecting water to come through your pipes between 11:00 p.m. and 6:00 a.m. this morning. I know that you all had a bit of a surprise, as well. But, we're all here and we're going to have a great day. So welcome. Welcome to the Pediatric Advisory Committee Meeting. Walt, you want to get started with the introductory comments?

DR. ELLENBERG: Sure. Good morning everybody. I'm Walt Ellenberg, I'm the designated federal official to the Pediatric Advisory Committee, and I'm going to read the opening statement for today's meeting and after I read my statement, I'm going to go around table and do formal introductions and Geoff will have some words and then we'll move on to the meeting agenda accordingly. And so, let me begin my statement.

The following announcement is made to address the issues of conflict of interest with regard to today's discussion. Of the reports by the agency as mandated by the Best Pharmaceuticals Act, Our Children's Act, and the Pediatric Equity Act. Based on the submitted agenda for the meeting, and

all the financial interest reported by the community participants, it's been determined that those individuals who will be participating in each topic do not have a conflict of interest for the following products: Differin Lotion, Dulera Inhalation Lotion Aerosol, MultiHance Injection, Nasonex, Natazia, Omnaris Nasal Spray, Protonix, Tamiflu, Taxotere, Viread.

And the committee will also receive at the end of the day information update from FDA with regarding their KidNet project that's ongoing, pilot study.

Tomorrow, which is Tuesday May 8th, the Pediatric Advisory Committee will meet regarding the Pediatric Focus Safety Reviews with regards to Gardisil, MENVEO. And at the end of the day we have several products that will be presented during the abbreviated products session of the meeting. And at that time the designated leaders of the Pediatric Advisory Committee, who have been screened for potential conflicts of interest, will present the following products of the FDA, but there will be no discussion of those abbreviated products. The products are Isopto Carpine, Zylet, and Zymaxid.

In general, the committee participants are aware of the need to exclude themselves from the involvement and the discussion of topics if their interests would be affected, and their exclusion will be noted for the record. Today Dr.

Wiefling will be participating as the Consumer Representative, Amy Celento will be participating as a Patient Family Representative. Dr. Mark Hudak will be participating as the Health Care Organization Representative, and Dr. Brahm Goldstein will be participating as the Industry Representative.

In addition the following expert consultants will be participating as temporary voting members today. Dr. Mink, Dr. Hewitt, Dr. LaRussa, Dr. Glasier, Dr. Raimer, Dr. Hudak, and Dr. Joad. Upon conducting conflict of interest analysis for all individuals participating in today's meeting, there were a number of individuals who will need to be recused for various topics throughout the day. And we will prompt each member and representative at the table to make sure that they know that it's time to slide away from the table.

The recusal means that the member will simply slide away from the table and will not participate in the discussion and will not be able to vote. Dr. Hewitt will be recused from the discussion and voting for Dulera, and Dr. -- I'm sorry and Nasonex. Dr. LaRussa will be recused from the MENVEO. Dr. Santana will be recused for Viread, and Dr. Raimer will be recused for Protonix, Taxotere, and Natazia, Dulera, and Gardisil.

With respects to all other participants, we ask that in the interest of fairness, that they address any current or

previous financial involvement with any firm whose product they may wish to comment on.

Later this morning we will have limited, open, public session and then scheduled to begin at 11:30. The copies of the material that were presented that will be presented at this meeting are available online. For members of the committee, I would just like to remind you please make sure that your turn on your microphones when you wish to speak and then turn off the microphones when you're finished. I think there's probably a load of three or four that can be open simultaneously, so if you just open and close your mics, that's the best way and you won't have any feedback.

I also request everybody at this time just to make sure that your cell phones are on mute, and that you're Blackberries are on mute. And at this time we will turn it back over to Geoff and then we'll move it to Dr. Murphy.

CHAIRMAN ROSENTHAL: Hold on while I mute my Blackberry. The -- often I get started with these introductory statements and Dr. Ellenberg follows, but I tend to say things that he says so today he went first. But first, you know, I'll take a moment before we get started to thank each of you for working hard with Dr. Ellenberg and with others in the office around the conflict of interest issues. This is always a challenge. It's just quite a lot of work for everybody, but

it's very important to the purity of our process, so thank you all very much for that.

The other thing that I say is we will have, be having a couple of breaks at different times, we'll be breaking in the morning, breaking at lunch, et cetera, and I'd like to ask everybody to please refrain from discussions of the topics at hand during those breaks. It's in the spirit of the work that we do with this committee, even at the FDA, that the ideas that come up around these topics are shared, that we maintain discussions in a transparent way. So please refrain from discussing the topics from the meeting, but bring up all ideas, any ideas, no idea is too off-the-wall to discuss in our open proceedings in this committee. So thank you very much for that.

And so, for the next step, Dr. Murphy is up at the podium already, so Dr. Murphy will take it away going over the agenda.

AGENDA OVERVIEW AND
AWARDS TO THE PAC MEMBERS

DR. MURPHY: Thank you. Before I do that though -- thank you -- before I do that though I do want to take moment and tell everybody that tomorrow you will be participating in our 200th product review and we have invited Dr. Rosenthal to help us write an article about this, and we did the first 100, actually, but it was so many years ago, and in half the time; it took us six years to do a hundred and we've done another hundred in three years.

So for those of you who have participated in the committee we invite to provide your comments and insights to Dr. Rosenthal because we would like to make this article a little different than the last one. It was just a compilation of what we'd learned and what the contributions the committee had made. We would like him to give a perspective of being on the committee and what your perspective of serving on this committee as far as the benefits to the public are.

And we're always interested in what suggestions you have on how to improve the process. Can't do anything about the water, so [laughs] we try to foresee everything, but some things we can't.

Well today is a bit of a sad time for us because a lot

of veterans are going to be leaving this committee, and we want to recognize them for their contributions, so I'm going to ask them to come up and receive a plaque which is given to each member along with their certificate recognizing their contributions to the Food and Drug Administration's efforts to ensure the safety of products that your children are using. Dr. Motil, would you please come on up and receive your plaque?

[applause]

Dr. Goldstein, Brahm?

[applause]

I think it tested first. Product testing, thank you.

[laughter]

Alex Rakowsky, Dr. Rakowsky.

[applause]

And most -- the person that we interact the most with is the chair. And the chair has a few extra responsibilities and it's really important that the chair represent not only you but try to convey to you the things that we might want to try to convey to you, and you've done a wonderful job in helping us with this designated review, in which Geoff has helped a lot in getting that done. And so Geoff Rosenthal is going to retire as our chair, but he's a been a wonderful chair and I would very much like to say how much we're going to miss him, and, of course, you're never free of us; I want all of you to know that;

we have a way of reaching out and asking you to contribute. Geoff, thank you very much.

[applause]

Geoff would like to tell you a little bit about the person who has been asked to replace him as our new chair. Thank you, then I'll go over the agenda.

CHAIRMAN ROSENTHAL: So I just have a few comments before I leave, you know, it's not that I love being in front of a microphone but you shouldn't pass up an opportunity probably first to thank people when given the opportunity, so I want to just quickly run through some of the people who have been influential and the work that has been done on this committee during the time that I've been on it. And I think I started in 2006, and I was granted an extension so I've had a fairly long time here, I've gotten a chance to meet many people. I won't be able to mention everybody by name, but there are a number of people who stand out as just real work horses in the name of pediatric public health in this context.

These would include members of the Office of Pediatric Therapeutics and members of the Pediatric and Internal Health staff in Cedar. Honestly, all the different drug divisions have had people involved, each of the centers, the Center for Drugs, Biologics and Devices, have had representatives that have come and helped us in our mission.

Specifically, I want to -- well before I go through some of the physicians, I want to make sure that I acknowledge Walt Ellenberg who has been my wingman for the last couple of years, and Walt has just done a great job in terms of keeping me on task. My wife would tell each of you that it's difficult to keep me on task, and Walt has done that.

But also, Sheila -- Sheila Reese, Unika, Joseph, Pam Weinel, Amy Odegaard, Betsy Sanford and Brenda Harman [spelled phonetically], these are the people who have done all the background, or much of the background work to put these meetings together.

In addition, we have had a great deal of help from the medical officers and from the staffs from the different offices that I had mentioned previously; so I want to thank the medical officers of which there are many, and have been many over the years.

We've had wonderful federal partners, from CDC, from NIH, from other federal organizations who have come to the table to help us clarify issues so that we can make the best decisions and the best recommendations around; pediatric public health, and this context. And so I'd acknowledge them too.

At this table we've always had industry representatives, and representatives from families, and patient groups, and consumer groups, and I have to say that their

comment shave just been invaluable as we've gone through this process as well. So I want to acknowledge all of them, and the committee members as well.

It never ceases to amaze me what phenomenal work can be achieved when you put a bunch of bright people around the table. I always have felt lucky to be at the table with all of you because you are incredibly bright and insightful and everybody together, I think, has come up with some great reflections on some of the questions that we've been asked to reflect upon.

But I also want to thank a few other people. Anne McMahon has been around for a lot of the time, or all of the time that I've been here, she's been very helpful. Bill Rodriguez, Harry Saks, Lisa Mathis, I haven't seen Lisa today but she's been very helpful over the years. Judy Cope has also kept me on track as well as everyone else. Skip Nelson, I want to acknowledge Skip because I think the work that Skip does in the context of the ethics subcommittee, of the Pediatric Advisory Committee, has really been important.

You know, as medicine and technology move ahead, the -- you know, our ethics, the way that we think about how we apply these medicines, these technologies, these study designs have to move ahead as well, and I think that Skip and the absolutely brilliant people that he brings to the ethics subcommittee

meetings have really moved a field of pediatric bioethics forward by leaps and bounds.

And finally I want to acknowledge Diane Murphy who, you know, for every high-functioning team there is a leader, there is a person who carries the torch when others are tired, there is a person who really kind of embodies the principles that drive the mission, and I see Diane being a person. I feel like completely honored to have worked with you, Diane, over the years. I think that the children of our country, really around the world, have benefited from you drive and from your focus and you know, on their behalf, I'm very appreciative of your work in this regard. So thank you so much.

All right, so it's also my pleasure to introduce to you guys, everybody the next chair. Ken Towbin has been asked to be the chair of the Pediatrics Advisory Committee once -- well starting at the September 2012 meeting.

And I'll just tell you a bit about Dr. Towbin. His addition to the Pediatric Advisory Committee has just been a wonderful addition. He's the chief of Clinical Child and Adolescent Psychiatry in the emotional and development branch in the Intramural Research Program at NIMH. Dr. Towbin has extensive and diverse experience in child and adolescent psychiatry. He received his AB from Cornell University and his medical degree from the University of Colorado.

He completed his general psychology residency training at Yale and his fellowship training in child and adolescent psychiatry at the Yale Child Studies Center. He then completed a two-year clinical psychiatric research fellowship at Yale School of Medicine. Dr. Towbin was on faculty at Yale as an Associate Professor and became Associate Director of Training and Clinical Director at Riverview Hospital for Children.

In 1993 Dr. Towbin came to the Children's National Medical Center to become the director of the residency training program in child and adolescent psychiatry and he became the professor of psychiatry and behavioral science and pediatrics at GW Medical School. He was the medical director for complex medical disorders team at Children's National Medical Center.

He's authored a number of papers focusing on issues around Tourrette Disorder, obsessive compulsive disorder, autism spectrum disorders. His current research interests follow his affiliations with Doctors Daniel Pine and Ellen Leibenluft at NIMH in the intramural research program focusing on the phenomenology and treatment of child and adolescent onset bipolar disorder, severe emotional deregulation, and anxiety disorders.

He is a diplomat of the American Board of Psychiatry and Neurology in both general psychiatry and in child and adolescent psychiatry. He's a fellow of the American Academy of

Child and Adolescent Psychiatrist. He's a clinical professor of psychiatry and behavioral science, still, at GW School of Medicine. And he's a reviewer for every relevant -- I'll just -- I'm saving some time -- every relevant journal in his field.

Now, two things. One is that I could give you more information, but the version of his CV that I got was redacted, and so I'm not able to provide you with further details. But the other is one of the reasons that I think it's great that Dr. Towbin is going to be the chair of this committee is that he has shown himself to be a great facilitator of discussion and a great enhancer for the exploration of scientific ideas as well as social impact and impact on families. And so I think that perspective will bring a lot to the chair, and I'm quite happy that you're going to be following me in this position, so thank you very much.

[applause]

DR. MURPHY: Thank you very much, Geoff. It's been a wonderful -- yeah, take the plaque.

CHAIRMAN ROSENTHAL: Just a few more words, no [laughs].

DR. MURPHY: [laughs] I'm not going to read the agenda to you. So what I did want to point out, though, is we will be doing both the abbreviated and the designated review abbreviated, and I think Walter's explained that to you. We

will begin in the morning with Tamiflu, which if you've been on our committee for a while you've seen this product before. It has had extensive reviews. And we will be having our public hearing session before lunch. We don't have many people signed up. And so what that's going to result in is you're going to have an extended lunch. We can't -- we'd like to start earlier, but we've told the divisions to be here at a certain time, so I'll let Walt handle the details of that as we get closer to lunch, but I wanted to let you know that we really cannot move the afternoon sessions up earlier. So thank you all, we look forward to your conversation today.

CDC: EPIDEMIOLOGY IN INFLUENZA IN CHILDREN AND CLINICAL COMPLICATIONS

CHAIRMAN ROSENTHAL: All right, well, let's move ahead with the agenda. Mr. Tim Uyeki from the Centers for Disease Control and Prevention is here to talk to us today about complications of influenza in children, including neurological manifestations and influenza-associated deaths in the U.S. Dr. Uyeki is chief medical officer in the Influenza Division of the National Center for Immunization and Respiratory Diseases at the Centers for Disease Control and Prevention in Atlanta. He's worked with CDC on the epidemiology, prevention, and control of influenza in the U.S. and worldwide since 1998.

He's a graduate of Oberlin College and he received a master's degree in public policy and in public health from the University of California at Berkley. He received a medical degree from Case Western Reserve University in Cleveland and completed residencies in pediatrics at the University of California in San Francisco and in preventive medicine at UCS Berkley.

He's also completed a two-year applied epidemiology fellowship in the Epidemic Intelligence Service at CDC and he's board certified in pediatrics and in preventive medicine and he's licensed and practices medicine -- or he's licensed to

practice medicine in California and Georgia.

In addition, he's an associate clinical professor in the Department of Pediatrics at UCSF and is an adjunct associate professor in the Hubert Department of Global Health at the Rollins School of Public Health at Emory. He's served as a consultant to the World Health Organization on clinical and epidemiologic issues related to seasonal, zoonotic, and pandemic influenza, including extensive international H5N1 outbreak experience for the World Health Organization and CDC in several countries.

He's also coauthored a number of papers and he serves the academic community as a thinker, investigator, writer, and reviewer. So without further comment, we're very pleased that you've come to join us. Thank you so much.

DR. UYEKI: Thanks very much for that kind introduction. Good morning. What I'm going to try to talk about this morning is to talk about the epidemiology of influenza in children, focused primarily on data from the U.S. And I'm going to talk about more severe disease resulting in hospitalizations and deaths. I'm not really going to focus on the overall burden and overall outpatient visits, but really focus on more sever disease. I'll talk about some clinical complications. I really want to focus more on neurological manifestations associated with influenza. Oh, I have no

conflicts to disclose.

So hopefully some of you will know some of the material I'm going to cover. We don't test every patient that present with influenza in the U.S., and those that don't present, so we have to do modeling studies to estimate the burden. We estimate that in the whole -- of all ages that there is an average of more than 200,000 hospitalizations that are attributable to influenza per year. The highest rates are in persons 65 years and older, although there are very high rates in very young children. The younger the age, the higher the hospitalization rates.

There are also high hospitalization rates for persons with chronic underlying conditions. This is another way of looking at -- this, again, is estimated influenza, attributable hospitalization rates per 100,000 persons by age group. And so the highest hospitalization rates in the US are in persons 65 years and older. They're also somewhat increased in persons 50 to 64 because of the prevalence of underlying chronic conditions. And you can see they're also higher in children less than 5 years of age.

Now, that was estimated influenza attributable hospitalizations. That's not lab-confirmed. We used surveillance data. This is data from our emerging infections program. A number of states participating in this. This is

actually laboratory-confirmed influenza. And this is hospitalization rates per 10,000 children. This is only -- this broken down by age group. So what you can see from this is consistently over five influenza seasons in the U.S., the highest hospitalization rates are in children less than six months of age consistently. The next highest rates are in children six to 23 months of age. And the older the child is the lower the hospitalization rate. So, again, the highest hospitalization rates, lab-confirmed influenza, are in the youngest-aged children.

Now, in the pandemic, recall that the highest hospitalization rates for seasonal influenza are typically in 65 and older. Well, it was not the case in the U.S. You can see the highest hospitalization rates were indeed in young children. And that was lab-confirmed data.

Now, this is also lab-confirmed data. Just to show you during the pandemic this is the hospitalization rates for children less than 5 years of age compared to other seasonal influenza epidemics. Generally higher, except for the 2003-2004 season, which was one of the most severe influenza epidemics we've had in about 30 years. But when you get to school aged children, 5 to 17 years of age, the hospitalization rates during the pandemic were far higher than what we see during seasonal influenza epidemics because, generally, we see rather low

hospitalization rates in the five and older age group. And this, again, is lab-confirmed hospitalizations.

Here's some data from the pandemic: 345 children hospitalized. Median age six years. Three percent died. Two-thirds had at least one chronic condition. And of those admitted to a PICU, again, 27 percent. Pretty high. Independent risk factors for admission to the PICU or death, having congenital cardiac disease or having cerebral palsy or developmental delay.

When we look at infants aged less than 1 year old, with 2009 each one in one, admitted to a neonatal intensive care unit or pediatric intensive care unit in California, 77 infants. The median age was a little more than three months. About a -- a little more than a third were less than 36 weeks gestation. About 60 percent of these had at least one chronic underlying condition, 45 percent required mechanical ventilation, 9 percent mortality. Pretty significant impact.

When you look at children in the U.S. admitted to pediatric intensive care units, this is 35 pediatric intensive care units throughout the United States, 838 critically ill children, median age of six years, majority with at least one chronic condition, but note that 30 percent were previously without a chronic condition. Two-thirds required mechanical ventilation. This was a pretty profound impact. Almost 9

percent mortality. Again, this is 35 PICUs throughout the U.S.

This is the epidemiology of hospitalizations -- lab-confirmed hospitalizations. What we see in a seasonal influenza epidemic. This is the year after the pandemic, the -- this is last season. The highest hospitalization rates, again, 65 and older, young children pretty high relative to other age groups. And if we look at this season, which is a relatively mild season in the U.S., so all the hospitalization rates are a bit lower, still the highest hospitalization rates are in persons 65 years and older, and the next highest is in young children. That's lab-confirmed data from the U.S.

Here's five seasons of data, lab-confirmed, seasonal influenza hospitalizations in the U.S. Just to show that underlying conditions in children, laboratory-confirmed influenza, febrile seizures, neuromuscular disorder, seizure disorders. These are children hospitalized with complications of influenza.

This is this current season laboratory-confirmed influenza. Neurologic disorder. We see this both in adults and children. Children are in the green here, the lighter color, but look at almost 50 percent with no known underlying chronic condition. Now, many of these are very young children.

What about mortality? Well, we estimate through modeling studies a wide range of influenza-attributable

mortality, and this ranges from about 3,300 during mild seasons to about 49,000 in a very severe seasonal influenza epidemic. It's a really wide range of estimated deaths in the U.S. attributable to influenza. But similar to hospitalization rates we see the highest mortality rates in people 65 years and older and it's pretty high with other chronic diseases, particularly pulmonary and chronic cardiac disease.

This is another way of looking at the mortality data. This is estimated, again, through modeling. Influenza-attributed mortality rates by age group, rates per 100,000. Again, the highest mortality rates are in people 65 years and older. Pretty low for other groups.

What about for children? Well, we don't have great data prior to 2003, we just have modeling data, and that estimated that an average in the U.S. of 92 influenza-related deaths in children less than five years occur every year. And note that this is the highest number for a vaccine-preventable disease in the U.S. in children.

Now, we had a very severe seasonal epidemic in 2003-2004, which we had enhanced surveillance. This was sort of done on an emergency basis. And we had 153 pediatric influenza-associated deaths that were laboratory-confirmed reported to CDC. Now, of these 153 deaths the median age was three years. About two-thirds were less than 5 years of age. About 50

percent had an underlying condition. Rather astonishingly, about a third died at home or in an emergency room suddenly. Few children had been vaccinated. We also found that the highest influenza-associated mortality rate was in the less than six months old. And as you got older -- the child got older, the mortality rate decreased. I just call your attention to underlying -- to clinical features of these pediatric influenza-associated deaths, altered mental status, and seizures. And note that there were encephalopathy cases. There were nine fatal encephalopathy cases that we reported in this case series.

Now, because of this experience -- again, it was a very severe influenza epidemic. Pediatric influenza-associated deaths in a U.S. resident became nationally notifiable to CDC, and we started this in the 2004-2005 season. And we basically had, before the pandemic, a range of about 46 to 88 children with laboratory-confirmed influenza deaths reported to CDC. Last season we had 122.

This kind of shows -- again, this is the 2003-2004 season. Here's when it became a nationally notifiable condition. This is during the pandemic: more than 300 laboratory-confirmed influenza-associated deaths.

Just some quick data from the pandemic deaths. The median age was more than 9 years of age, but wide -- included children of all ages. About 72 percent were older than 5 years

of age. It included all racial and ethnic groups in the US. The median time for an illness onset to death was seven days, and the location of death -- although many died in the pediatric intensive care unit, many also died in the emergency room or outside the hospital, and a majority of these pediatric deaths occurred before pandemic vaccine was available. So 84 percent were not vaccinated. And, of course, children less than six months are ineligible.

Just to show some of the medical complications. Although respiratory are the primarily complications, note seizures in 33 percent, encephalopathy, encephalitis diagnosis in 5 percent. Again, a majority had high-risk, chronic conditions. Note neural development disorder 60 percent, seizure disorder 33 percent. Also note that 27, or 9 percent, were previously healthy. And we did see, of those that had a sterile site specimen that was tested for a bacterial co-infection, of those tested 29 percent did have evidence. And so, unfortunately, the typical pathogens we see with influenza complications, staph aureus, both MSSA, but more MRSA, Pneumococcus, and group A strep.

And what we did see during the pandemic was the highest mortality rates were actually -- were very high in -- not in people 65 and older, but in people 50 to 64. And this is not broken down further, this is less than five, but I'll tell

you that the rates -- the mortality rates in the less-than-six-months were very high.

But we really don't know how many people died because at some point we stopped having laboratory-confirmed deaths and hospitalizations reported to us during the pandemic. It overwhelmed the states and really there was no point in doing all the testing. So we've done modeling studies to estimate this.

I'll just draw your attention to children. We estimate during the pandemic 20 million illness cases. That doesn't consider asymptomatic infections as illness: 87,000 hospitalizations in children and look at this. Although we had more than 300 deaths in children reported, we estimate that there were over 1,200 deaths in children.

So this is what we've seen in terms of pediatric deaths. Again, a big spike during the pandemic. Last season 122. We've actually -- this is what we published on our website on Friday: 20. We've had a few more reported, and so I'll just give you a quick update. This is preliminary data. Don't quote this but the median age is seven years. Again, majority with an underlying chronic medical condition. Median duration of illness, seven days with a wide range. In children who had no underlying medical conditions it's a rather rapid time from illness onset to death, five days. In those that have

underlying medical conditions it's longer. And, alarmingly still, a lot of children dying outside the hospital or pronounced dead in the emergency room. And although many had respiratory complications, particularly pneumonia, note, of this year's deaths -- again, it's a small number to date. It's been a mild season. We've had 20 percent of these deaths reported as encephalopathy or encephalitis.

Now, here's some -- again these are preliminary data. This is cumulative since the 2004-05 season: 817 children who have died of laboratory-confirmed influenza in the U.S. This is rather alarming from my perspective. Median age, seven years. Again, a majority had underlying medical conditions. Note that underlying neurologic conditions there's a range of 18 to 40 percent of the cases each season. The median illness duration is five days. There were more than a third that a rather fulminant course up to three days from time of onset to death. In children who had no underlying medical conditions it's four days to death, and those who had underlying conditions it's longer median time to death. Location of death. Again, still a lot of children overall dying outside the hospital or in the emergency room. And -- although respiratory complications are primarily the cause of death, note that invasive bacterial co-infection in 38 of those tested. And, again, seizures, encephalopathy, encephalitis in about 9 percent. So, you know,

a lot of neurologic complications here.

So I'm just going to give a quick summary of some complications, particularly neurologic now. There's a wide spectrum of influenza virus infection, ranging from asymptomatic infection to uncomplicated illness, but I'm going to really focus now on severe complications, not so much moderate complications such as otitis media or sinusitis, but more severe complications that result in hospitalization or death. And typically in children and adults that's -- the most common is actually exacerbation of underlying chronic disease. But clearly influenza virus infection can cause or can trigger an inflammatory response resulting in pathology and certainly the role of co-infections, including bacterial co-infections, are important.

So these complications influenza in children clearly include respiratory and typically pneumonia, which can be both viral or secondary bacterial. But certainly rare cardiac complications have been reported, including myocarditis and pericarditis, myositis. But let me just go into neurologic complications. So there's a very wide spectrum of neurologic manifestations associated with influenza, and that ranges from actually simple febrile seizures to very transient encephalopathy for a few hours to actually fulminant progression to rapid death. And just some of these more severe

complications include encephalopathy and, as a subset of that, acute necrotizing encephalitis, which is the worst aspect of that. There are strokes, there are subarachnoid hemorrhages, I think people are familiar with Reye syndrome and the association with aspirin.

But there are other more severe complications such as ADM, transverse myelitis, Guillain-Barre syndrome is very rare in children but it's more common in adults as a complication of influenza virus infection. We tend to think about it as a complication -- rare complication of a vaccination, but in fact it can be associated with infection.

Febrile seizures. Okay, just -- it's a frequent cause of febrile seizures during influenza season. In Hong Kong, some data. It's a significant cause of hospitalizations. That's been reported during peak months of more than a third of febrile seizures in Hong Kong hospital admissions were associated with influenza. Here's the U.S. data from the Children's Hospital of Philadelphia. Over four influenza seasons, 744 children with lab-confirmed influenza, 12 percent had underlying neurologic or neuromuscular disease. Some of these included cerebral palsy, hydrocephalus, seizure disorders. And this study found that having neurologic or neuromuscular disease was independently associated with developing respiratory failure. And so underlying neurologic disease is a risk factor for more severe

complications, particularly respiratory.

Here's more data from the Children's Hospital of Philadelphia. They looked at neurologic complications: 72 had influenza-related neurologic complications, 56 of those had seizures, but eight had acute encephalopathy. Typically very young children. And the median time from illness onset to onset of encephalopathy, 1.5 days. Very fulminant. And some of these characteristics included disorientation, lethargy, visual hallucinations speech abnormalities.

So what are the presentations of influenza-associated encephalopathy? Well, it's typically a history of brief, influenza-like illness and upper respiratory tract illness. So it's typically with high fever and onset of upper respiratory tract symptoms. Very short time from onset of influenza illness to onset of encephalopathy. We see confusion, altered speech, mutism, irritability, hallucinations, lethargy, somnolence, hypertonia, coma. We see seizures, we see rapid deterioration. You can go into shock. And we typically see increased intercranial pressure.

Most of the data reported on this syndrome has been from Japan, where they've been doing surveillance for many, many years. It's national surveillance. Note that in this one large series, 80 percent had onset of encephalopathy within two days of onset of influenza onset. Majority of these cases were

children less than five years of age. The peak age group was those aged one year. There was very high mortality or neurologic sequelae reported in this case series. Almost 32 percent died. Again, that was data from the late 1990s. And here's other clinical features: 80 percent of those children had seizures. But look, also hallucinations and abnormal behavior in a smaller subset.

The worst form of encephalopathy is in acute necrotizing encephalopathy, also called acute necrotizing encephalitis. This is not necessarily specific or unique to influenza, but it is frequently reported with influenza. The extreme abnormalities found on neuroimaging. I'll show you some of that later. This has been reported in Asian countries, it's been reported worldwide in other countries, including the U.S. We're very high in mortality or outcomes such as permanent sequelae.

So here's just some data from Taiwan. I'll just note that of these children with neurological complications, none had been treated with antivirals before the onset of their neurologic disease: seizures, 43 percent, lethargy, altered mental status, visual hallucinations, hypersomnia, personality change, speech disorder, loss of consciousness, abnormal behavior, impaired consciousness, disorientation. A whole range of neurologic manifestations.

Now, Japan has national hospital-based surveillance for this condition. It's the only country. We do not. Japan estimates a range of 50 to 200 cases per year, depending upon the severity of the influenza season. We have no idea about the occurrence or frequency of this incidence in the U.S. because we don't have national surveillance. The only thing we did was, during the '03-'04 season, which was very severe, we reported nine cases, these are fatal cases, of encephalopathy among 153 children that died overall.

But what we have is -- and this is unpublished data and I think those of you who were on the committee back in 2007 have heard a more extensive presentation of this. I have one slide to summarize. We also asked states to report encephalopathy cases to CDC. Of these, we teased out 42 influenza-associated encephalopathy cases reported from 22 states. The median age was five years, included all age groups. 64 percent were previously healthy children, 18 full recovered but nine died. So pretty severe. Again, that's during a seasonal -- a pretty severe seasonal influenza epidemic. But we get these cases every year.

And here's just some data from that '03-'04 season showing the -- of the suspect and probable cases we classified. The majority had onset of encephalopathy less than three days from illness onset of their influenza illness.

This is just a neuro image. This is an MRI image. This is a 5-year-old fatal case from a girl in Michigan from 2003, and note the bilateral inflammation, thalamic lesions. This is classic for acute necrotizing encephalitis, and this child unfortunately progressed in 24 hours from onset of her encephalopathy to brain death and herniation. And here's a case from the U.S., published in Pediatric Infectious Disease Journal. Again, with the same bilateral thalamic inflammatory lesions. That child actually recovered but had some sequelae. We had cases of encephalopathy reported from all over the world, including in the U.S., during the pandemic.

And I'll just note this is one case in a child from the US, southern -- southeastern part of the U.S.:12-year-old, previously well girl, one-day history of fever, diarrhea, weakness, altered mental status. She progressed to herniation, brain death. Here's her MRI showing the classical bilateral thalamic lesions. I asked her brain tissue to be sent to CDC. This correlates the same areas. Necrotic lesions. We were -- we tested -- my colleagues tested her brain tissue for influenza by RT-PCR in a viral culture. We were unable to demonstrate any influenza, and this is typical. This is not invasion of the central nervous system tissue by influenza virus infection. The pathogenesis is believed to be an inflammatory cytokine-triggered pathogenesis.

So just to conclude, one last slide to say that -- I think just to remind people of the association between influenza in children and aspirin in Reye syndrome. However, it can occur without aspirin ingestion and is -- occurs more commonly with influenza B than influenza A, but, you know, it's a pretty profound syndrome and we have seen a dramatic decline in cases of Reye syndrome associated with influenza since the Surgeon General's warning in 1982 not to use aspirin in children.

So just to conclude, I hope I've presented data -- I apologize for the speed of it but I hope I presented data to convince that young children are at very high risk for severe influenza complications that can result in hospitalization and death with either seasonal or pandemic influenza and that there is a wide spectrum of neurologic manifestations associated with influenza virus infection that can be very transient, that can also be very severe. And children -- this can occur in children with underlying neurologic conditions, but also previously healthy children. And most of these neurologic manifestations, they can be transient or they can be persistent. They can occur -- they usually occur with fever during the early course of influenza onset -- influenza illness onset. And this often occurs without or before antiviral treatment is initiated. And influenza-associated encephalopathy and encephalitis occur both with seasonal influenza and with pandemic influenza in children,

and the clinic progression can be very fulminant. The outcomes can range from full recovery to neurologic sequelae to death, and it's my impression that this entity is greatly under-recognized and under-detected in the U.S. For many reasons we don't have surveillance. So thank you very much.

CHAIRMAN ROSENTHAL: Thank you, Dr. Uyeki. We do have a few minutes for questions for Dr. Uyeki, but before we do that I forgot to go around the table and have people introduce themselves. So let's do that before questions and then we'll just do that briefly so everyone knows who everyone else. Dr. White, can you just get us started, please?

DR. WHITE: Michael White, Ochsner Clinic, New Orleans, I'm a pediatric cardiologist, chair of our IRB, and director of ethical education for University of Queensland, Ochsner Clinical School.

DR. HUDAK: Mark Hudak, chairman of pediatrics, University of Florida, College of Medicine, Jacksonville.

DR. MOTIL: Kathleen Motil. I'm a pediatric gastroenterologist from Baylor College of Medicine and I have -- my training in nutritional biochemistry and metabolism.

DR. HEWITT: My name is Geri Hewitt. I'm an OBGYN in Department of Pediatrics and the Department of OBGYN at Ohio State College of Medicine in Columbus, Ohio.

DR. WIEFLING: Hi, my name is Dr. Bridgette Wiefling.

I’m an internal medicine and pediatric physician and the CEO of the Anthony Jordan Health Center, which is a federally-qualified health center in Rochester, New York.

DR. MINK: My name is Jon Mink. I’m a pediatric neurologist and chief of the division at the University of Rochester, also in Rochester, New York.

DR. GLASIER: I'm Charles Glasier. I’m a pediatric radiologist and pediatric neuroradiologist at Arkansas Children’s Hospital in the University of Arkansas in Little Rock, Arkansas.

DR. LARUSSA: My name’s Phil LaRussa, pediatric infectious diseases, Columbia University, New York.

DR. RAIMER: Sharon Raimer. I’m chair of dermatology at the University of Texas, Galveston, and I specialize in pediatric dermatology.

MS. CELENTO: Amy Celento, patient and family rep.

DR. JOAD: Jesse Joad, pediatric, pulmonary professor emeritus [spelled phonetically] from the University of California, Davis.

DR. KRISHER: Good morning. Jeff Krischer, professor epidemiology and biostatistics, the University of South Florida at Tampa.

DR. TOWBIN: Kenneth Towbin, per Dr. Rosenthal’s generous introduction I think you’ve heard quite enough about

me.

CHAIRMAN ROSENTHAL: Geoff Rosenthal, professor of pediatrics at the University of Maryland, and I'm a pediatric cardiologist.

DR. ELLENBERG: Walter Ellenberg, designated federal official, Office of Pediatric Therapeutics, FDA.

DR. WAGENER: Jeff Wagener, professor of pediatrics, University of Colorado, pediatric pulmonary.

DR. RAKOWSKY: Alex Rakowsky, IRB chair at Nationwide Children's Hospital in Columbus, Ohio.

DR. SANTANA: Good morning. Victor Santana, pediatric hematologist, oncologist at St. Jude Children's Research Hospital in Memphis, Tennessee.

DR. GOLDSTEIN: Good morning. Brahm Goldstein. I'm a pediatric intensivist and the industry representative and professor of pediatrics at University of Medicine and Dentistry of New Jersey.

DR. REED: Good morning. Congratulations, Mr. Chairman. My name is Michael Reed. I'm a professor of pediatrics at New Med [spelled phonetically] and I'm director of clinical pharmacology and toxicology at Akron Children's Hospital.

DR. COPE: Judy Cope, Office of Pediatric Therapeutics, FDA. My background's pediatrics and adolescent

medicine, and I'm also an epidemiologist.

DR. SACHS: Hari Sachs, team leader of pediatrics on staff. Good to see everybody. I'm a general pediatrician who still sees patients.

DR. MURPHY: Dianne Murphy. Office director, Office of Pediatric Therapeutics, FDA, and my background's pediatric infectious disease.

DR. LEWIS: Linda Lewis, medical team leader in the Division of Antiviral Products, FDA. I'm trained as a pediatric infectious disease specialist.

DR. MARCUS: Kendall Marcus. I'm a deputy director for safety in the Division of Antiviral Products and my background is adult infectious disease.

DR. HAUSMAN: Ethan Hausman. I'm a medical officer in the Office of Surveillance and Epidemiology in the Division of Pharmacovigilance. My training's in anatomic and clinical pathology, transfusion medicine, and pediatrics, and I'm also on staff at Georgetown Hospital for pathology and pediatrics.

DR. GADA: Neha Gada, pharmacist and safety evaluator in the Division of Pharmacovigilance.

DR. CAO: Kelly Cao, safety evaluator, team leader in the Division of Pharmacovigilance, FDA.

DR. BORDERS-HEMPHILL: Vicky Borders-Hemphill, drug-use data analyst in the Office of Surveillance and Epidemiology

in FDA.

CHAIRMAN ROSENTHAL: Thank you. And, Dr. Mink, I saw your hand go up for a question for Dr. Uyeki.

DR. MINK: Yeah. Two questions. That was an excellent presentation, thank you. You addressed this for acute necrotizing encephalopathy. I wonder for the other neurologic complications if you have any estimate about percentage is due to direct infection of the brain by the virus and what percentage is due to a parainfectious inflammatory component. And the second question is do you know the most recent report of Reye syndrome associated it with influenza in the United States?

DR. UYEKI: Second question, I do not. I would say that I have -- you know, we don't do surveillance for that at CDC. I have been consulted on some cases over the last 10 years. The last one I was consulted on was actually in a adolescent, but I don't recall -- it's not been in the last five years, but I can't answer the second question.

First question, in terms of all these neurologic manifestations and complications associated with influenza, they're generally not associated with detection of virus in the CSF. I'll say that there are -- if you search the literature you will find some studies from Japan in which there were -- RT-PCR was positive on CSF. There were some cases reported in the late 1990s and early 2000s and this was an actually very

controversial issue.

I think in general the dogma is -- in general -- that this does not represent virus being present or infecting the central nervous system. Having said that, as full disclosure, I am the coauthor of a case series published in Pediatrics, probably in 2004 with colleagues from Baylor, in which one of those -- if you go back -- it was I think a case series of eight children with neurologic complications. One of them was a six-month-old in which Baylor colleagues isolated influenza virus from CSF. I do not understand that case -- the pathogenesis of that case.

And as you probably are aware, there have been multiple hypotheses postulated for this. And in the animal model people have postulated ascension up the olfactory nerves. In general, we don't think that happens in humans. Other people have suggested viremia and invasion -- breakdown the blood-brain barrier. But I think most of the compelling data is from Japan, which suggests cytokine dysregulation. So it's virus infection of the upper respiratory tract triggering the cytokine dysregulation, so you see the patient in shock, very high fever, actually you can see sometimes hypothermia, and you do see these inflammatory lesions and high cytokine levels in the CSF.

I think it's not definitively worked out but it's more likely to be not virus invasion of the CNS. It's -- sometimes

we see in these children an associated pneumonia, but generally it's an upper respiratory tract infection.

CHAIRMAN ROSENTHAL: Okay, we're slightly behind schedule. We've got a couple other questions. Dr. Santana and then Dr. Rakowsky.

DR. SANTANA: You presented -- I think it was an American series of about 140 patients or so, and then you made a comment -- this was I think hospitalizations and you made a comment. "About 80 percent of them had not been vaccinated and ergo 20 percent were." So can you remind us, in general terms, what does vaccination do to the course of the disease in children?

DR. UYEKI: So -- do you mean with neurologic complications --

DR. SANTANA: Yeah, with complications in general.

DR. UYEKI: So -- well, specifically for neurologic complications there are no data -- no studies that I am aware of that have assessed the effectiveness or efficacy of influenza vaccination to reduce or prevent neurologic complications. But certainly we have plenty of data on the -- you know, randomized controlled studies or in effectiveness studies to look at the reduction, the prevention of influenza vaccination to reduce influenza-like illness or lab-confirmed influenza. That's going to vary from year to year depending on many factors, and

especially including the antigenic match between circulating strains and vaccine.

So it's hard to generalize but we would think that if you prevent influenza illness or you prevent influenza virus infection, you will reduce complications. And I think that includes reducing the most severe complications. Unfortunately, influenza vaccination, as you're aware, is not 100 percent efficacious or effective, and that is why we do see some severe outcomes, including, unfortunately, some children who die of influenza virus infection or are hospitalized with a more severe disease. But in general there is benefit in vaccination of reducing both illness and complications, as well as infection.

DR. SANTANA: But for neurologic it's unknown, that's what I heard you say at the beginning, right?

DR. UYEKI: Yeah. Specifically for neurologic complications I am not aware of any study that's actually specifically assessed that.

CHAIRMAN ROSENTHAL: Okay. Three more quick questions. Dr. Rakowsky, Dr. LaRussa, and then Dr. Joad and then we'll move on.

DR. RAKOWSKY: Hope this is a quick question. Thank you for a very, very nice presentation. For children with acute encephalitis, I know you broke it down to major past medical history issues, but is there any data that these children have

higher rates of rheumatologic conditions, persistent asthma, severe eczema. In other words, are these proinflammatory kids --

DR. UYEKI: Yeah.

DR. RAKOWSKY: -- in general that could have had this response?

DR. UYEKI: That's a great question. Can't answer the question. The data haven't looked at that that I'm aware of.

CHAIRMAN ROSENTHAL: Dr. LaRussa.

DR. LARUSSA: So, without virus in the CSF, you start to look at things that are either different about the virus or different about the host. And have you started to collect and compare, let's say, 2009 H1s that -- H1N1s that caused neurologic complications, compare them to ones that don't, or look at the hosts in terms of genome-wide studies to see if you can start to unravel the risk for the cytokine-mediated pathogens.

DR. UYEKI: Great question. Totally agree with you. Would love to do those studies. Wish we could have funding, wish we could have all the academic resource power to do these. These need to be done. These kind of host genetic studies should be done. They're very complicated. But it's not just for neurologic complications. Should be for children who die, especially those who have no underlying disease who don't die of

bacterial coinfection, just pure fulminant influenza virus infection in a previously healthy kid, whether it's neurologic or not. Just a viral pneumonia or shock. So I'd like to see those done. I'd like to have the funding. I'd love to do the studies. I'd like to be very involved. Let's do it.

CHAIRMAN ROSENTHAL: Dr. Joad.

DR. JOAD: I was curious about the hallucinations in the disease itself in the absence of a antiviral, and I notice that you have that listed. Is it a prominent symptom? Did anybody walk in the street, get hit by car, based on it? In the natural disease -- in the disease influenza.

DR. UYEKI: It's a great question. So what I've presented is most severe cases. What I have not presented are -- and I can tell you this anecdotally. And it's not fair to really comment on anecdotal data but I've done so many consultations over the years with, you know, colleagues of yours and so forth across the U.S. and, you know, during the peak of influenza season you and your colleagues are working in the emergency room will have seen children who just have transient encephalopathy who will have hallucinations for a few hours and it self-resolves. Those are not what I'm reporting, so we have no idea what the frequency of mild, you know, transient -- I'm only presenting what's been published. More severe data. So really can't answer that question. I wish we could. And I

think it's -- you know, this is somewhat like tip of the iceberg, but generally these are caught in the first couple of days after the onset of influenza illness with high fever.

And in the U.S. -- in general we are not a country -- it happened more during the pandemic but it's gone down since the pandemic, where we have kids that are taken right away to medical care within the one to two days of illness onset and are treated with antivirals. It doesn't happen in this country. It happens in Japan.

So although there's still plenty of children with influenza, including severe complications, who are not treated with antivirals in the first, you know, early part of the illness onset. So that's why I can say, you know, without presenting data to you, my feeling is that these are occurring in the U.S. without or before antiviral treatment. Can I give you data? No, we don't have data on this, but it's a different situation than in Japan where -- many factors. They take kids to present to medical very quickly, there's national health insurance, clinicians are aware and they're treated early. It's a different situation than this country.

CHAIRMAN ROSENTHAL: Thank you, Dr. Uyeki. Thank you very much.

DR. UYEKI: Thank you.

CHAIRMAN ROSENTHAL: All right.

SURVEILLANCE OF ADVERSE EVENTS ASSOCIATED

WITH OSELTAMIVIR IN A HEALTHCARE CLAIMS DATABASE

CHAIRMAN ROSENTHAL: Next speak will be Dr. Andrew Mosholder. Dr. Mosholder is a child and adolescent psychiatrist who initially worked at FDA on the premarketing evaluation of new psychiatric drugs, and after completing a master's in public health he transitioned into his current position as medical officer in the Office of Surveillance and Epidemiology in the Division of Epidemiology, too.

In 2009 he also served on FDA's response team for the H1N1 influenza pandemic and he will speaking with us about a project that he did in -- that he worked on in that context, surveillance of adverse events associated with oseltamivir in the healthcare claims database. So thank you for coming to talk to us today, Dr. Mosholder.

DR. MOSHOLDER: Thank you very much. My pleasure to be here. And after that very fine presentation I'm going to shift the focus a little bit more to Tamiflu, the drug under discussion, and just take a few minutes to summarize this project we did as surveillance during -- it was initiated during the pandemic, as was mentioned.

And just by way of background, as everyone knows, we had the pandemic, which -- the strain was susceptible to the

neuraminidase inhibitors, oseltamivir and Zanamivir, so we really had unprecedented levels of use of the neuraminidase inhibitors during the pandemic and we decided to undertake some enhanced surveillance activities for safety outcomes. And part of that effort was leveraging an existing research contract to access data on these antivirals from a large healthcare research database.

But by way of preface, there have been previous observational epidemiologic studies of oseltamivir. Most of them that appeared in literature were actually sponsored by Roche, the manufacture of Tamiflu.

And just to summarize briefly, a number of these showed fewer respiratory complications with oseltamivir treatment compared to patients who received no antiviral for their influenza. There's one study -- let me use the pointer here. There's one study that showed fewer cardiac adverse events. And in general they reported fewer neuropsychiatric events, although there was one study that showed actually an association -- positive association with episodic mood disorders in oseltamivir being more frequent than with untreated influenza.

There was also a Department of Defense study which showed, again, a reduction in neuropsychiatric events with oseltamivir treatment versus untreated influenza. So the

purpose of this project was to conduct surveillance for safety. Adverse events of interest with the neuraminidase inhibitors using the OptumInsight Healthcare Claims Research Database. This was formerly the Ingenix Research Database.

And to tell you some about the database, it's a private insurance medical claims dataset, also includes pharmacy claims data and in some cases laboratory results, although that wasn't relevant to this project. The medical claims are a mixture of inpatient and outpatient visits and emergency department visits. The outcomes are in the format of diagnostic billing codes from the ICD-9 and also pharmacy claims, including only outpatient prescriptions, but for our purposes here, since neuraminidase inhibitors are primarily outpatient setting drugs, that wasn't too much of a drawback.

Just to give you a sense of the database, as of 2006 there were data on 14 million individuals. Relatively few have -- or are over age 65, as is typical for private insurance databases because of availability of Medicare above age 65, and the database tends to represent the Southeast and Midwest geographic regions. There's a specific application, analytic tool, that was developed for this database known as a pario [spelled phonetically] and it actually creates propensity-matched samples for one-to-one comparisons of patients taking two drugs of interest that are being compared to each other.

And it involves a sample of patients who have at least six months of baseline data prior to the prescription or the event of interest. So this allows some descriptive information on the patients who are receiving the drugs, and also allows analysis of selected inpatient or outpatient diagnoses which appear in the record following the prescription or the event of interest. And the data's maintained anonymously for privacy considerations.

Turning to this specific analysis. We wanted to have a sample of influenza patients either with or without antiviral treatment. So the patients all had one of these two ICD-9 diagnostic codes in their record for influenza. Now, the treatment patients had a five-day prescription for neuraminidase inhibitor, plus a diagnosis of influenza on the day of dispensation. And, as you know, I think these drugs can be used prophylactically with a 10-day course, so that was in an effort to make it more specific to treatment of acute influenza by limiting it to a five-day prescription. The untreated influenza patients had the diagnosis but no antiviral within a week. And we created cohorts of oseltamivir for treatment versus untreated influenza, and that's what I'll be emphasizing today.

We also looked at Zanamivir for treatment and also still undergoing analysis in a oseltamivir-Zanamivir comparison. So we selected categories of adverse events that were of

interest with neuraminidase inhibitors. Neuropsychiatric colitis, dermatologic thrombocytopenia, other bleeding conditions, and also respiratory complications relevant to influenza. And we emphasized newly-observed outcomes, meaning that the diagnosis had not appeared in that patient's record in the previous six months. And we analyzed the risk window with a follow-up up to 30 days after the prescription of interest or, in the case of untreated, after the diagnosis without a prescription.

As I mentioned, the pario tool creates a propensity score of matched cohorts. We decided, however, to subgroup on the pediatric age group after matching, and I'll be emphasizing results from that age group. Then relative risks with 95 percent confidence limits were computed. It's important to note these were not corrected for multiple comparisons, so this should be regarded as exploratory rather than a priori hypothesis testing. And the timeframe was October 2007 through September 2009, so I think people will see that this gives a mixture actually of seasonal influenza and, later in the dataset, pandemic influenza.

Okay, turning to the results. First, this gives an overview of the basic patient characteristics. You see this has been sub-grouped. The pediatric age group here and the adults on the right. You'll see first, working from the bottom up, the

racial composition, although there was a lot of unknown ethnicity for the subjects, but where it was known there's fairly good balance.

As I mentioned, the South region was predominant. Gender was pretty evenly balanced. The one issue we had where there was a lack of balance was in the age groups. And we see here that the oseltamivir group on the left was 93 percent above -- or age 10 and above, whereas just over half of the untreated influenza was actually patients below age 10.

So I'll show you how we tried to deal with that in a few slides. But first, just to show the results for adults. You see here the selected outcomes on the left and the numbers of patients with those outcomes in their records as newly observed diagnoses and the relative risks and confidence limits. And basically you see there weren't any associations with any of these selected outcomes identified in the adult age group.

Looking at the pediatric age group now, and here I'm showing it sub-grouped by age, zero to nine and 10 to 17, to try to deal with that imbalance I mentioned. You see that there're actually very few oseltamivir-treated patients in the sample under age 10. But at any rate, in the younger age group there really weren't any associations identified. There was I guess an elevated point estimate for neuropsychiatric events, but it was based on a very small numerator of only a single event with

oseltamivir. In the older pediatric age group we did see reductions in some of the respiratory-related events, and in fact otitus media and this other respiratory category had confidence limits that excluded one.

Also pneumonia relative risk were reduced below one point estimate, which is not statistically significant. And a somewhat higher-risk estimate for colitis, again based on very small numbers and not significant. Because of the interest in neuropsychiatric events with oseltamivir we wanted to drill down on those. More specifically, this shows this list of specific ICD-9 codes that went into the neuropsychiatric category. And it's basically convulsions and then the remainder were more typically sort of purely psychiatric events, if you will.

Now, I should mention, this is -- some of the published literature used a much broader definition of neuropsychiatric, where they included things sort of fundamentally neurological complications as well as psychiatric events, so this was a little more narrow maybe than some of the published literature.

So, okay, here we're looking at under 18 age group and you see for any event they were numerically more frequent with oseltamivir but not statistically significant. Convulsions, again, numerically more frequent but very small numerators and far from statistically significant. We did see an imbalance

with more frequent episodic mood disorders, again very small numbers however. And a little bit lower rate of anxiety-related disorders. For depressive disorder not also classified we did have a relative risk of about three, which was statistically significant. But because of that age imbalance we had a concern, which is that to the extent that this age group has younger kids which might be less apt to be diagnosed with a psychiatric disorder than, say, adolescents we wanted to sub-group it further.

So as I mentioned before, in the zero to nine with oseltamivir they actually only had a single event, which was a convulsion. And for the 10- to 17-year-old subgroup I'll show you those results on the next slide. So here are the same neuropsychiatric outcomes that we just saw, but now limited to 10- to 17-year-olds. And, again, you see overall there weren't any associations found. We did see elevated risk ratio for depressive disorder not elsewhere classified and episodic mood disorders, but not statistically significant. And a lower point estimate for anxiety-related disorders.

So to wrap up, first we need to keep in mind the limitations of this kind of analysis. First of all, this was exploratory, as I mentioned. The statistics were not adjusted for multiple comparisons. Also, these outcomes were all in the health care claims data, they were not validated by any kind of

chart review. And, importantly, and Dr. Uyeki touched on this, too, that if some of these psychiatric events are transient they may not be captured or may not result in a health care claim and one can imagine that a child might have a severe behavioral abnormality lasting for a few hours, but if it doesn't result in a visit to the physician or the emergency department it wouldn't necessarily be visible to this kind of analysis. And, of course, we have the small sample size so few don't know if -- how the results might have differed if we'd had more of a sample, of course.

So to sum, we didn't find any clear indication of any previously unsuspected adverse reactions to oseltamivir. We saw some reduction in some respiratory-related conditions. In contrast to some of the published literature, we didn't see a reduction in neuropsychiatric events. And, as I mentioned, we did see higher frequencies of certain selected mood disorder diagnoses, but the inferential meaning of these is uncertain for the reasons I mentioned.

And I just want to conclude by acknowledging our collaborators at OptumInsight, Donna Funch, Arnold Chan, Betsy Cardstein [spelled phonetically], also my colleagues in the Office of Surveillance in Epidemiology, Elizabeth Maloney, and our director Judy Staffa, director of Division 2 of Epidemiology. So -- and with that I can take questions or

whatever people would like.

CHAIRMAN ROSENTHAL: Thank you. Dr. LaRussa?

DR. LARUSSA: So, I have to think about this a little bit more, but, you know, we always worry that the patients who got treated are different than the ones who didn't get treated. It would be a third of maybe just taking the treated person -- people and doing either a self-controlled case series or a risk interval analysis with a shorter risk window to see if you can figure out whether the events are truly associated with the drug or not.

DR. MOSHOLDER: That's a very good idea. We haven't undertaken that, but that -- but a case crossover-type design of that nature, one there's the -- the hypothesis is that there's very rapid onset of these kinds of events might be a productive approach, so thanks for that comment.

CHAIRMAN ROSENTHAL: Dr. Krisher.

DR. KRISHER: In order to ask you I have to turn my back to use the microphone. I'm sorry. Just a quick statistical or epidemiological footnote here. So, it's important to adjustments for multiple comparisons only when you're concerned with the type one error. And since there wasn't anything significant here, type one errors are really not an issue, so I wouldn't worry about that piece. What you really do have is inadequate power to actually see a difference. And

that's really affected by the very low incidence rates or actually, more specifically than --

CHAIRMAN ROSENTHAL: Dr. Krischer --

DR. KRISHER: -- number of bases in the denominator.

CHAIRMAN ROSENTHAL: Better for you to -- Dr. Mosholder will understand if your back is to him, but better for you to speak into the mic.

DR. KRISHER: So the epidemiology -- the analysis here, it's interesting data but it's -- there's really some issues in terms of the analysis that ought to be addressed in this presentation and the previous one. So, first, the whole issue of multiple comparisons. Not really relevant. Multiple comparisons have the effect of increasing type one error. That is to say, you'll find some spurious significant associations when none really exist. In this case we didn't see any statistically significant associations so the issue of adjustments is really moot.

The other problem is the type two error, and that's really the issue here, and that is affected very much so by the very low incidence rates. So essentially the number of cases that any of one of these things is so low that there's really not adequate power really to see a difference between treated and untreated populations, even if there was one. And so it's really interesting data but it really doesn't help you drive any

conclusions from that. In conjunction with the first presentation, you see the association with other chronic illnesses and age, which would imply that all of the subsequent analysis really need to be adjusted for that in some kind of analysis or covariance or a modeling effect, since that's likely to be the underlying principle in explaining what we're seeing here. So I would suggest that there are, you know, a few more steps along the way.

And then I'd have to remind everybody that we have to be very careful in the term association versus causality. You know, this is really confounded here in both presentations to a great extent. So it could be that individuals who have chronic illnesses are at higher risk for H1N1 or at higher risk for complications and adverse events, or -- you know, I guess I don't have to repeat that point, but essentially all we're really looking at is associations. And, in fact, the confounding of other chronic illnesses could explain very much of it -- all of these data. Thank you.

CHAIRMAN ROSENTHAL: All right. Thank you. Let's move on.

TAMIFLU (OSELTAMIVIR) SAFETY ASSESSMENT

VACCINE SAFETY DATALINK PROJECT, 2007-2010

CHAIRMAN ROSENTHAL: Our next speaker is Dr. Sharon Greene. Dr. Greene is a principal associate in the Department of Population Medicine and is an epidemiologist with experience in infectious disease surveillance and outbreak investigation. Her current research focuses on near-realtime vaccine safety surveillance, the use of space-time scan statistics and syndromic surveillance and trends in the use of antibiotics and antiviral medications. Prior to her joining the Department of Population Medicine Dr. Greene served as an EIS officer in the Enteric Diseases, Epidemiology Branch at the CDC. She has a PhD in epidemiologic science and an MPH in hospital and molecular epidemiology from the University of Michigan. And she will be talking to us on Tamiflu or oseltamivir safety assessment of vaccine -- using the Vaccine Safety Datalink project from 2007 to 2010. Dr. Greene.

DR. GREENE: Thank you. Good morning. This audience is very familiar with the background for this project regarding neuropsychiatric events, principally the reports, mostly from Japan, of psychiatric events including delirium, confusion, abnormal behavior, etcetera sometimes leading to injury and even death.

In March 2007, the Japanese Ministry of Health warned doctors not to prescribe oseltamivir to 10- to 19-year-olds and the FDA has updated the package insert to cover neuropsychiatric events. There have been prior U.S. cohort studies that have shown no or even protective associations with neuropsychiatric events in these various databases covering time periods from 1999 to -- as most recently as 2007.

The motivation for our study was that there is some uncertainty that remains around this question. Some of the available evidence does not support an association, such as the negative studies in the US and the fact that the neuropsychiatric adverse events that have been reported could be caused by influenza infection itself rather than the drug.

While other evidence does support a possible association, including those case reports mostly from Japan, as well as the characterization of the reported abnormal behavior not necessarily being consistent with typical influenza-related central nervous system complications. So we wish to confirm and extend the prior studies with particular attention to refining adverse event definitions and risk intervals and to take advantage of more recent data, including the pandemic when this drug was very widely used, and one would hope that it would become easier to observe and detect rare adverse events. Although, of course, I have to say power remains an issue. The

setting for our study is the Vaccine Safety Datalink, or VSD, project.

This project was established in 1990 and is a collaborative project among CDC and 10 medical care organizations, or MCOs, eight of which participated in our study. VSD routinely collects demographic vaccination and medical care data on over nine million members annually. And to support influenza surveillance activities, ancillary data files were created, including claims filled in the outpatient setting for antivirals, as well as laboratory test orders and results for influenza and RSV. This map shows the eight participating VSD MCOs. I'm located at the Harvard program site and America's Health Insurance Plans is the prime contractor.

This figure shows patterns of antiviral dispensings for treatment purposes within the VSD population from January 2000 through June 2010. The four different colors represent these four antiviral drugs, and you can see that the patterns change over time in response to the emergence of viral resistance and also during the pandemic.

The safety assessment period for our study is from January 2007 through June 2010 and this period, you can see, covers the great majority of oseltamivir use within our population and also happens to represent a period of date availability for all participating MCOs.

We used a matched cohort design, so you can imagine two patients who both have influenza diagnoses around the same time, one of whom receives an antiviral dispensing and one does not, and we test the null hypothesis that the risk of an adverse event, or AE, in this risk interval, is the same for patients with influenza who do versus do not receive oseltamivir within zero to two days of the index date.

Our study population included outpatients with influenza during this time period, and we identified almost 250,000 patients, around 62,000 of whom were ineligible, the majority because they were enrolled for less than one year, and we wanted to require a lengthy enrollment so that we could characterize underlying health conditions as well as markers of health care utilization; 2,000 were excluded because of a history of chronic kidney disease. This condition can affect the rate of clearance of the drug from the body, which can affect the definition of risk intervals. So for a cleaner analysis we excluded these patients.

We excluded over 700 patients who had a late antiviral dispensing, so three to nine days after the index date. We excluded patients who received zanamavir, amantadine, or rimantadine, or they received oseltamivir but the dosing was inconsistent with treatment purposes, so not a five-day supply or if the data interval was not 10 units dispensed. And one

patient had incomplete data. So this left us with an eligible cohort of 187,000 patients. The way the patients entered into our cohort, the great majority entered because they had a diagnosis of influenza, so ICD-9 code 487-488, the great majority were in the clinic setting. An additional 14,000 were identified because of an influenza diagnosis in the emergency department.

Several thousand more individuals did not have influenza diagnoses, but they did have positive tests for influenza, mostly by RT-PCR, also viral tissue culture, and a few 100 patients were detected because of rapid test or DFA/IFA. If a patient happened to have both an influenza diagnosis and a positive test, they entered the cohort only once via diagnosis, and when I refer to an index date, I mean the influenza diagnosis date or the specimen collection date that led to the positive test.

So we have this eligible cohort and then we identify patients who received oseltamivir within zero to two days after the index date and that was 15 percent of the patients, and the remaining 85 percent received no antiviral during that period.

There were a number of factors that greatly increased the probability of oseltamivir treatment in the eligible cohort. So being during the pandemic period greatly affected the probability of treatment. Also, patients who had a history of

asthma were more likely to be treated as well as those with markers of utilization including history of influenza vaccine, having been in the highest quartile of outpatient visit frequency in the prior year, having a Charlson comorbidity score greater than zero. And also the probability of treatment varied markedly across the different medical care organizations.

So we have our identified treated and untreated patients and we did propensity matching leaving us with 27,684 matched pairs, half of whom were treated, half of whom were not.

This shows our neuropsychiatric adverse event definition. We looked at ataxia, psychiatric events. These were the events of greatest a priori interest and include some of the psychotic mental disorders -- delirium, delusion, depression, suicide, et cetera. Also looked at ICD-9 codes for encephalitis and disturbance of consciousness.

For most diagnoses we looked at all settings, so clinic, ED, and inpatient, but for encephalitis we only looked at inpatient and ED. We had two definitions for each adverse event, an incident definition similar to the newly observed events in the prior presentation. So here we only counted an ataxia diagnosis after the index date if it was the first such ataxia diagnosis for that patient in at least one year. For the psychiatric and disturbance of consciousness adverse events we extended that period for two years because we really wanted to

exclude patients who had ongoing treatment for an existing disorder.

In addition we looked at bringing in non-incident events, so we only counted an ataxia adverse event after an index date if it was the first such ataxia diagnosis for that patient in a shorter period of only 42 days. So this helps us look at exacerbations of underlying conditions in recurrent events.

Here are some additional adverse event definitions we looked at, including arrhythmia, syncope, convulsions, movement disorder, and stroke, and their settings, and again we had an incident adverse event definition and a shorter non-incident event definition.

Regarding the risk intervals that we used for all of our adverse events, the primary definition was the one to seven days following dispensing, and this was shorter than those used in most other studies. And we decided to do this because the duration of treatment is brief, it’s only five days, and the half-life of the active metabolite oseltamivir carboxylate is six to ten hours, suggesting that related adverse events are unlikely to be attributable to the drug beyond three days after the last dose.

We also developed two secondary risk interval definitions. We extended the window to one to 14 days to

accommodate delayed presentation or diagnosis, and also a very brief one to two days o the index date, and this was from several of the reports of the neuropsychiatric events happening with abrupt onset and rapid resolution after a single dose of oseltamivir. And also the longer you follow these matched pairs, their comparability diminishes over time, for instance, due to treatment effectiveness or nonadherence and a very short risk interval can help eliminate that problem.

For our analyses we built propensity scores using variables we believed to be potentially associated with both the exposure and at least one of the outcomes. We checked the balance of all measured baseline covariates, then individually matched patients who were treated and not treated and conducted a conditional logistic aggression analysis.

The variables that went into our propensity score included age in these categories: sex, which influenza season it was, markers of health care utilization in the prior year, so whether they had influenza or pneumococcal vaccine, the frequency of outpatient visits and hospitalizations, whether they had any vaccine in the week after the index date, and also their Charlson comorbidity index.

In addition we included indicators of 15 high-risk conditions for severe influenza disease using ICD-9 codes in the year prior to the index date, each of them yes/no. We also

included having a history of any of the adverse events as well as a history of three negative controls in the prior year. We also included in the propensity score, was the medical care organization or MCO and interaction terms between MCO and every other covariate I mentioned except for post-partum and ataxia history, which was not possible because the frequency of those was very sparse.

We then assessed covariate balance. The purpose of this was to assess the fit of the propensity score or PS model. So before matching all covariates we wished to be balanced between oseltamivir-treated and the no-antiviral groups conditional on the propensity score. And after adjusting for PS, we did achieve balance, meaning that we had nonsignificant associations from high-score tests after we stratified on propensity score vision tiles or 20 propensity score strata. So it was nonsignificant for all covariates except for one, pregnancy, which was significant a point or two. However, one would expect by chance for the nominal alpha level of .05 and 37 covariates included in the propensity score model, two might be significant by chance alone.

So ultimately we believe that our propensity score model was indeed reasonable. We then proceeded to individually matched pairs by MCO within plus or minus two weeks of the influenza index date, by age, such that infants were matched

with other infants, one to 19-year-olds were matched within plus or minus two years, and greater than 20-year-olds were matched within plus or minus five years, also matched by sex and propensity score, using the nearest neighbor. And after matching there were no important differences observed in the distribution of measured confounders between treated and untreated patients.

So some results, these are results for the incident events for our primary risk interval of one to seven days following the index date. Here's each of our adverse events within our 27,684 matched pairs, the numbers of events which in the treated and nontreated categories, the odds ratio and the 95 percent confidence interval. And you can see that none of the lower bounds of the confidence interval exceeds one, none of the odds ratios are particularly concerning. We do have small counts. We have limited power. But I will note that psychiatric events, which was our event of a priori greatest interest, was the most frequently observed event, and we can look into, break this category down further.

So for our incident psychiatric diagnoses there were 35 in the oseltamivir-treated group for a rate of .13 percent and 29 in the untreated group, for a rate of .10 percent, and this shows the ICD-9 codes and the counts for the treated and untreated groups. And by far the most common diagnosis in both

groups was anxiety state unspecified, accounting for over half of the outcomes in each group.

The next most frequent category was depressive disorder not elsewhere classified. This apparent numerical imbalance of ten versus five is interesting in light of the prior presentation. I will also note, however, that there are additional depressive diagnoses in the untreated group further down in the chart in the 296 range. So, once we take that into account it doesn't seem so much that depressive disorder is unbalanced. You do see additional diagnoses for psychosis, delirium, anxiety, and there were no diagnoses for suicide or self-inflicted injury.

Now, moving to the secondary risk intervals, so when we extend the risk interval to one to 14 days or shortened it to one to two again, there is nothing significant and there's no elevated odds ratios, et cetera. We have extremely small numbers. When we extend to also bring in the non-incident events and to look at exacerbations or recurrences we have, of course, more counts, but still it's very balanced between the treated and untreated groups. And there were very similar results for the secondary risk interval.

So this is the result for the one to seven days. When we look at the one to 14 days or the one to two days again we see no elevated odds ratios, no statistically significant

associations.

We also conducted subgroup analyses. Here's incident neuropsychiatric event frequencies for the 10-19-year-olds, which is the age group for which Japanese regulators have contraindicated oseltamivir and again, small counts, but we have no, nothing of great concern here. We also extended this subgroup analysis to two 19-year-olds. This was to pick up the less than 10-year-olds due to a recent increase in abnormal behavior reports among oseltamivir-treated less than 10-year-olds in Japan. But again, there's no imbalance between the treated and untreated groups.

Similar limitations to this study as a prior study this is electronic data only. We could not control for some of the factors that influence the probability of whether a patient receives treatment, such as influenza disease severity upon presentation, the time since symptom onset, and the BMI. Nor could we measure some factors that would definitely influence the outcome, such as whether the patient was adherent to treatment, whether they had exposures to other medications other than influenza antivirals. Our adverse events are not chart validated. We had to assume that patients who are ostensibly unexposed were truly unexposed, but we could've missed dispensings to patients who had limited pharmacy coverage.

Some of our study exclusions may limit

generalizability to some patients, so we did not include in our study patients who received oseltamivir without a detectable influenza episode. So if they presented at the clinic and had any diagnosis other than influenza and got the drug, we did not include them. Nor did we include patients who received the drug through a telephone dispensing protocol. We excluded patients who had delayed dispensings, patients with chronic kidney disease, and patients receiving oseltamivir for prophylaxis. So, our, in conclusion, our study provides no evidence for an increased risk of incident or nonincident, neuropsychiatric or other adverse events, within biologically plausible risk intervals following oseltamivir treatment, and this is consistent with prior U.S. cohort studies.

The psychiatric adverse events were the most frequently observed outcome, but they were observed no more frequently in the treated versus matched untreated patients. And we also observed no elevated risk in the pediatric and adolescent subgroup analyses.

I would like to thank my collaborators at CDC and across all the participating medical care organizations, and thank you for your attention.

CHAIRMAN ROSENTHAL: Thank you very much. Let’s, may we ask you questions about your talk when we, after we’ve heard the next two as well?

DR. GREENE: Sure.

CHAIRMAN ROSENTHAL: So we have, now on our schedule we have time for a 10-minute break. We're running 10 minutes late, but let's take the break anyway and try to resume at 10:00, which is actually nine minutes from now. Thank you.

TAMIFLU (OSELTAMIVIR PHOSPHATE): BACKGROUND INFORMATION AND DRUG UTILIZATION PATTERNS

CHAIRMAN ROSENTHAL: All right. Let's start to move back towards our seats so we can continue with our program. Thank you very much. So, our next speaker will be Amy Taylor. Dr. Taylor attended medical school at Howard University and concluded her pediatric residency at Madigan Army Medical Center in Tacoma, Washington. She has a master's of health science and health policy from Johns Hopkins. She has been on the team at the FDA for the last five years. She has contributed much over my time on this committee, and so we're, I'm very pleased to introduce Dr. Taylor for discussion of Tamiflu, specifically background information and drug utilization patterns.

DR. TAYLOR: Thank you. As it says here I will present the background drug information and utilization patterns for Tamiflu. This is an outline of my presentation. Tamiflu or oseltamivir is an influenza neuraminidase inhibitor. The drug is available as oral capsules as well as an oral suspension. It's been marketed by Hoffman La Roche, Inc. Tamiflu was originally approved for marketing on October 27, 1999. It was granted pediatric exclusivity on March 22, 2004. The pediatric labeling changes related to this presentation occurred on

February 22, 2010. As you can see here, Tamiflu is indicated for the treatment of influenza in patients one year and older who have been symptomatic for no more than two days. Prophylaxis, also for prophylaxis of influenza in patients one year and older. There are some limitations of use that are included in the labeling. It is, efficacy is not established in patients who begin therapy after 48 hours of symptoms. It's also not a substitute for an annual influenza vaccination. There's no evidence of efficacy for illness from agents other than influenza viruses type A and B, and also you need to consider available information on influenza drug susceptibility patterns and treatment effects when deciding whether or not to use Tamiflu.

In 2009 Tamiflu received an emergency use authorization. This was due to early in the 2009 H1N1 outbreak the secretary of health and human services declared a public health emergency. WHO subsequently declared a pandemic. FDA staff at that time reviewed all available PK and safety data in infants less than one year of age. Remember that it was not approved at that time for infants less than one year. Emergency dosing recommendations were developed for infants and discussed with the sponsor and CDC. An emergency use authorization, or an EUA, was issued April 2009, and the dosing recommendation for treatment and prophylaxis in infants less than one year of age

were disseminated. FDA requested that the sponsor specifically track serious AEs in the subgroups expected to experience dramatic increase of Tamiflu use, and this would be pregnant women, infants less than one year of age, and the elderly. In June 2010 the emergency was deemed to be resolved and the EUA was terminated.

This slide provides information on dosing for Tamiflu. The next few slides that I'll go through provide information on the safety labeling for Tamiflu. The highlight section includes warning and precautions, and they -- it contains two warnings dealing with the serious skin hypersensitivity reactions, as well as the neuropsychiatric events.

Tamiflu is contraindicated in patients with known serious hypersensitivity to oseltamivir or a component of the product. Severe allergic reactions have included anaphylaxis and serious skin reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme.

There are four warnings and precautions in the labeling starting with the serious skin and hypersensitivity reactions. In section 5.2 the neuropsychiatric warning gives information about influenza-associated events, as well as events associated with Tamiflu use. This is what's currently in the labeling. There is also a warning concerning bacterial infections, as well as information about the limitations of

populations studied.

In clinical studies, the most common adverse reactions in adults and pediatric patients 13 years and older were nausea, vomiting, diarrhea, and abdominal pain. In patients one year to 12 years, the most common adverse reactions were vomiting, diarrhea, otitis media, and abdominal pain.

There have been several clinical studies in pediatric patients with Tamiflu. The most recent clinical trial was a six-week uncontrolled pediatric seasonal prophylaxis safety study in patients 1 to 12 years of age. This study was of 49 patients. I will note that over the years over a thousand pediatric patients have participated in various clinical studies with Tamiflu. This was just one small safety study. In this safety study there were no deaths or serious adverse events. The adverse events were consistent with those previously observed. This information, as I show here, has been added to the labeling.

I will now discuss drug utilization patterns for oseltamivir. From 2005 to 2011, approximately 20.2 million prescriptions were dispensed to 18.1 million patients; 7.7 million prescriptions and 6.9 million patients were aged 0 to 16 years. This slide provides graphic depiction of oseltamivir use by age. You'll note that the peaks associate with the flu seasons each year, and you'll see a very large peak, of course,

at 2009. This slide provides information on cumulative drug use by age, and you'll see there that pediatric patients received about 38 percent of the prescriptions, as well as they were 38 percent of the patients.

The top-prescribing specialties were primary care providers, as well as pediatricians. Pediatricians accounted for 22 percent or 4.4 million prescriptions of the total prescriptions dispensed. The top diagnosis code in pediatric patients aged 0 to 16 years was flu with respiratory manifestations not elsewhere classified.

I'll now provide a brief summary of previous PAC presentations for Tamiflu. On November 18, 2005, a safety review for Tamiflu was presented one year after receiving exclusivity. At that time, we reported that we had eight pediatric deaths, 32 neuropsychiatric adverse events, and 12 skin or hypersensitivity adverse events. That caused the labeling to be revised to include precautionary language regarding severe skin reactions. At that time, the PAC agreed with FDA that there was insufficient evidence to establish that neuropsychiatric adverse events represented a safety signal. We were asked to follow up with the PAC after one or two additional influenza seasons and to continue enhanced monitoring.

On November 16, 2006, another safety review was presented focusing on the neuropsychiatric adverse events. At

that time we found that there were a total of 129 neuropsychiatric adverse events in pediatric patients. You'll see there the breakdown of those neuropsychiatric events. We had delirium, suicide events, panic attacks, delusions, convulsions, depressed level of consciousness, loss of consciousness, and then also miscellaneous. And based on this review of the neuropsychiatric adverse events, FDA initiated labeling -- a labeling change through negotiating with the sponsor and that was occurring at the time that the PAC occurred. We had a labeling update in November 2006, and at that point, language was added to the labeling that discussed our findings.

In November 2007, a cumulative review of neuropsychiatric adverse events and deaths in patients 0 to 21 years of age was presented. We found that -- we also presented a review of all antiviral drugs approved for treatment or prophylaxis of influenza. We also reviewed the literature describing neurologic and psychiatric complications of influenza in pediatric patients. At that time the pediatric advisory committee agreed with the FDA's plan to continue monitoring adverse events on a monthly basis during the flu season and recommended labeling change to reflect the neuropsychiatric symptoms associated with influenza.

And the next few slides will show that labeling

change. And I want to acknowledge the following people for their help with this presentation. Thank you.

CHAIRMAN ROSENTHAL: Thank you, Dr. Taylor, and we'll hold on questions for Dr. Taylor as well until after our next speaker.

TAMIFLU: REVIEW OF POST-MARKET REPORTS IN THE ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE ASSOCIATED WITH OSELTAMIVIR USE IN PEDIATRIC (0 TO 16 YEARS) PATIENTS

DR. ROSENTHAL The next speaker is Dr. Neha Gada. Am I pronouncing that correctly?

DR. GADA: Neha Gada.

CHAIRMAN ROSENTHAL: Neha Gada. Dr. Gada received her Bachelor's of Science in Pharmacy from the Ohio State University and her PharmD from the University of Washington. She completed a pharmacy practice residency at the VA Maryland Health Care System in Baltimore, and she'll be speaking today on a review of post-market reports in the adverse event reporting system database that are associated with oseltamivir use in pediatric patients.

DR. GADA: Thank you. Good morning, everybody. My name is Neha Gada and I'm here to discuss a review of the post-market cases with oseltamivir in the pediatric patient population. For the purpose of this presentation, pediatrics refers to those ages 0 through 16 years of age.

This slide shows a list of abbreviations I will commonly use throughout this presentation. Our adverse event reporting system, otherwise known as AERS, is the database that I'll be using for our case reports. There is a medical

dictionary for regulatory activities, otherwise known as MedDRA, that we use for coding of our adverse event reporting. The preferred terms, or PTs, are basic unit of the MedDRA dictionary that is very specific and self-descriptive that are terms that we use more for coding. There are several adverse events that I'll be focusing on and that include neuropsychiatric, influenza, encephalopathy, and cardiovascular events.

So what is AERS? AERS is a computerized database that contains spontaneous reports. It contains human drug and therapeutic biological reports. To date, there are over five million reports in AERS, and annually, we receive about 700,000 reports. There are several strengths and several limitations for the AERS database. Some of the strengths include that AERS includes U.S.-marketed products, include events in broad patient populations. It is useful for detecting events with a rare background rate. It may be useful for events that occur shortly after exposure. And it may be useful for detecting events not previously seen in clinical trials.

Some of the limitations of AERS include variable quality of reporting. For example, you may not have concomitant medications or no confounding disease states in the AERS reporting. From the duplicate reporting you may receive the report from multiple sponsors or multiple clinicians. There may be under-reporting. This is a passive surveillance tool. It

may be difficult to determine association due to the drug product based on the data that we have. And finally, there are reporting biases associated with our AERS database.

So the purpose of our review was to summarize the post-market AEs in children treated with oseltamivir from June 2007 through December 2011 using the AERS database. A comprehensive review of the adverse event profile of oseltamivir in pediatrics was performed and presented to the 2007 PAC. Hence, we chose dates in order to update that review, and so that's why we have our search dates from June 2007 through 2011.

This is how I'll plan to talk about our presentation. First, I'll discuss the serious unlabeled events. Next I'll discuss serious neuropsychiatric AEs. Finally, a review of the death cases and a subset of that including -- a subset population of the pediatric cases in the infant, and for the purpose of this review, that's defined as less than or equal to 12 months of age.

So first we'll begin with the discussion of the serious unlabeled events. The way we went about identifying serious unlabeled events was through review of the top reported PTs from all serious reports in our AERS database. This included a crude count of our AERS cases. This means that these cases were not adjudicated and they may include duplicate reporting. We also used data mining stratified by age to

potentially identify any new safety concerns. You'll see from this slide a snapshot of what we saw in AERS from reports from June 2007 through December 2011. We have the adult population, the pediatric population, the age unknown values, and then the total population. We have numbers for all reports, which includes both serious and non-serious reports, and then we have just the serious reports, and finally the death cases. As we can see in red, the pediatric numbers are listed.

The pediatric cases, including all serious and non-serious cases, represent about 28 percent of all cases reported with oseltamivir in the search date. This figure shows dispensed prescriptions in AERS reports in the pediatric patient population. On the Y axis on the left we can see the number of dispensed prescriptions in the thousands, and on the right we'll see the number of AERS reports in increments of 20. On the bottom we have the time period in quarters by year. So, as we can see, the two mirror each other closely. So in the bar graph we have the oseltamivir prescriptions dispensed and we can see the peaks during influenza season, including the peak in 2009 H1N1 pandemic year. Additionally, we see that the AERS reporting peaks closely mimic that.

So this table shows the top reported PTs for serious pediatric adverse events reported from June 2007 through December 2011. As I mentioned, as we saw earlier, there were

902 AERS cases, and this is a crude count number. So the top PTs are listed on the left-hand side, and we note that the neuropsychiatric terms and influenza disease related terms are the most commonly reported PTs. For example, we see abnormal behavior, convulsions, nightmares, screaming, as some of the neuropsychiatric events, and for some of the influenza disease related terms, we note pathogen resistance, ARDS, and respiratory failure.

Now I'll transition to discuss the neuropsychiatric events. We set forth to identify the country of report origin for neuropsychiatric AEs with oseltamivir in order to assess for geographic specificity. And this is because due to the labeling changes that occurred in February 2008, there is -- it is noted that most of the cases from that review that was presented to the 2007 PAC did come mostly from Japan. We will discuss the top reported PTs for neuropsychiatric cases, and finally, we took a closer look at our own cases from the United States from 2010 to 2011 and we'll discuss those.

So this line graph shows our AERS report crude count using the System Organ Class term, which is the broadest level of term in the MedDRA dictionary for nervous system and psychiatric disorders by year. We will discuss from the date of approval, from October 1999 through December 2011. We have three groups. The first group is the United States, all the

reports from the United States, which is in the blue line with a blue diamond. We have the foreign cases, which also include cases from Japan, in the green line with a magenta diamond. And finally our third group includes the cases from Japan, with a magenta line and the yellow triangle.

So, as we can see, the Japanese cases comprised mostly of the foreign case reports up until the pandemic year as they are overlaying on each other. Up and through 2007, the Japanese reports also represented the majority of pediatric neuropsychiatric reports on AERS. From 2008 to 2011, the number of U.S. reports rose, and this may be due to a couple of reasons, including the simulated reporting as a result of the labeling changes that went into effect in February 2008, as well as increased drug utilization, which occurred during the 2009 H1N1 pandemic season.

We also note that the foreign reports outside of Japan increased significantly during the pandemic year as well, which corresponds with greater drug utilization during this period. We also note that the Japanese reports after 2007 started to decline. This may be due to the Japanese restricted news in the pediatric patient population for ages 10 to 19; however, we did not have drug utilization data from Japan, so that limited our ability to draw any conclusions.

So summarizing the table that was discussed previously

for all serious pediatric events, this table discusses specifically the neuropsychiatric events. We used some very specific search criteria that can be found in the review, but it includes numerous PT terms related to neuropsychiatric event and numerous other high-level terms from the MedDRA dictionary. So, again, on the left-hand side of the column we see the preferred terms and on the right-hand side we see the count of PTs with the percentage of total. And now I want to just re-emphasize that the 600 case count is a crude count and this search date, again, went from June 2007 through December 2011.

So the majority of PTs are labeled, and the warnings and precautions are in the post-marketing section of the label, where we note that they are closely related to labeled terms. So the underlying terms are the terms that are not specifically found in the Tamiflu labeling, but as I mentioned, are closely related to label terms. That includes aggression, visual and auditory hallucinations, screaming, anger, and somnolence.

So overall we note that a review of the top PTs from the crude count of the neuropsychiatric event did not identify any new safety concern and we note that the Tamiflu labeling -- the current Tamiflu label adequately discusses these events.

So as I mentioned earlier, we took a closer look at the U.S. cases reported with the neuropsychiatric event. This is just for a two-year period from 2010 to 2011, and we

identified 26 cases. The age range is from two months to 16 years, and there was an equal distribution between males and females. We did not have any U.S. deaths reported due to neuropsychiatric event or to any other event in this small case series. We noted that the neuropsychiatric AEs are consistent with labeling and they included events such as abnormal behavior, delirium, and hallucination. Now out of the 26 cases, 24 of these cases were used for influenza treatment and two cases were used for -- the one case was used for influenza prophylaxis and then the second case was used for off-label use for RSV bronchiolitis. So I want to discuss those two cases.

The first case is from the United States and occurred in March 2011, and this is a consumer report that describes a 6-year-old female who reportedly experienced visual and auditory hallucinations intermittently for about 20 hours after receiving eight days of oseltamivir. It was reported that the patient remained afebrile during this time and continued to hear voices once oseltamivir was discontinued. Additional clinical information was not provided.

The second case occurred in February 2010 and this again, also a consumer report, in a 16-month-old female who experienced agitation, crying, and possible disequilibrium during treatment with oseltamivir for RSV bronchiolitis. She reportedly returned to her baseline status 12 hours after

discontinuing her last oseltamivir dose and, again, this is -- additional clinical information was not provided.

So now I'm going to transition to discuss the pediatric death cases. This, again, goes back to our broad search dates from June 2007 through December 2011. In order to do this I'm going to discuss our case characteristics followed by a discussion of the U.S. cases. I'll discuss the cases in which the reporter -- or which the case was coded as sudden death in in cases in which the reporter also reported the cause of death due to cardiovascular causes, and finally, in which -- cases in which the reporter attributed cause of death due to influenza encephalopathy.

So after revealing the pediatric death cases we identified 112 unique cases during this search date. The average age was 6.8 years with a range from 22 days to 16 years. The majority of the cases, or 38 of the 112 cases, came from Japan. Sixty-three of the cases came from other foreign countries, and 11 of the cases came from the United States. Of the cases with the known event date, we note that the majority of the cases came in from 2009 to 2011, likely due to the H1N1 pandemic string. The average times of onset from the first dose to death were 7.8 days with a range from zero to 58 days, and the duration of therapy averaged 3.8 days with a range from one to 12 days. The majority of the cases, or 109 of the 112 cases

reported use for influenza treatment, and three of the cases reported use for influenza prophylaxis. We will discuss these cases used for influenza prophylaxis shortly.

In order to capture a description of how sick these patients are we captured data to identify if they reported co-infection with pneumonia. We noted that 35 percent, or 39 of these cases reported co-infection with pneumonia. We also note that the majority of the cases resulted in hospitalization, with 85 percent of our cases resulting in hospitalization. Fifty percent, or 57 cases which is not listed on this chart, required ICU admission, and 38 percent required ventilation. So we can see that this is a sicker population.

The reported attribution for of the cause of death is listed on this table as well. I'm going to focus on the cases in greater detail in which the recorder should be that the cause of death due to neuropsychiatric event, cardiovascular reason; cases in which the report was coded with the term sudden death, and influenza encephalopathy.

So overall, a summary of the death cases, we noted that the cases were confounded by comorbidities and distinguishing drug event causality with oseltamivir was not possible. Some of these comorbidities included MRSA pneumonia, septic shock, ARDS, avian influenza, and multi-organ failure.

As I mentioned earlier we had three cases in which the

reporter attributed the cause of death due to neuropsychiatric event; however these same three cases were previously discussed and presented in the 2007 review and presented to the PAC at that time. The reason they came up during our search dates is because there are follow-up reports that were captured from our search dates. There's no new additional information provided in these cases.

I do want to point out that there were no deaths related to neuropsychiatric events in our case series. There are 13 deaths in which the reported attributed cause of death due to some sort of cardiovascular event. All these cases involved critically ill patients, and they all required hospitalization. Eight of the 13 cases came from Japan, one from the United States, and four from other countries. And the average age range -- or the age range was 14 months to 16 years. Of note a QT study reviewed in 2010 found no prolongation of QT intervals of therapeutic or supratherapeutic doses of oseltamivir.

Now I'm going to discuss the cases in which the pace required was coded with a PT sudden death. This is again from the Pediatric Death Case Series at large, and from June 2007 through December 2011. So all of these six cases occurred from Japan. They all required hospitalization, and they've all used -- oseltamivir was used for influenza in all of these six cases.

The age ranged from two to seven years, and of the six cases we had one case report in which an autopsy finding was reported. Three of these six cases reported a clinical diagnosis of myocarditis, two of the cases reported respiratory depression, and one of the two cases with respiratory depression noted pathology findings of marked congestion and swollen brain. This was consistent with influenza-induced disease. The remaining case noted complications of influenza, and the patient had thrombocytopenia and GI bleeding prior to drug use.

So in this -- in our death case series of 112 cases we had 15 cases in which the reporter attributed cause of death due to influenza encephalopathy. Most of these reports came from Japan, in which 13 of the 15 cases came from Japan, one came from the United States, and one came from France. The majority of the cases occurred during the 2009 H1N1 pandemic season. Of note, 11 of these reports attributed encephalopathy as due to influenza, or they noted that the ELG is unrelated to oseltamivir.

Of the four remaining cases there were two cases reporting Reye's syndrome, one with multi organ failure, and one in which the reporter did not have an attribution for cause of death listed. That case is from the United States, and it was -- and occurred in January 2011 in a three-and-a-half-year-old male who received two doses of oseltamivir, developed

hallucinations, abnormal behavior, and died either with or from influenza and encephalopathy. No causality assessment was made by the reporter.

So as I mentioned previously we have three cases in which the reporter -- in which oseltamivir was used for influenza prophylaxis. So I'll take a minute to discuss those cases now. Two of the three cases are from the United States, and they both reported confounding factors including either disseminated tuberculosis, or surgical complications of abdominal compartment syndrome. The next case is a foreign report, and this occurred in July 2009 in a 15-year-old female who had two negative influenza tests, and was discharged after a short hospitalization for assessment in influenza and pneumonia. She was discharged on a course of azithromycin for pneumonia treatment, and with oseltamivir for influenza prophylaxis. One to two days after hospital discharge she experienced septic shock, cardio-respiratory arrest with failed resuscitation attempts, and died upon -- and died at that time.

So that concludes the pediatric death portion of the review, and the last part of our review will involve the discussion of adverse events in the infant patient population defined as less than or equal to 12 months of age, and again, this is from June 27 through 2011. We identified 32 unique cases in the infant patient population. The most commonly

reported -- the most common reported events were neuropsychiatric-related, and we felt that these events are related or closely related to labeled terms.

I just wanted to back up for a minute. I want to point out that the reason that we looked at the infant population was because this was an unapproved patient population; however during the 2009 pandemic, the agency did approve emergency use for this patient population. And because of that and because of the bundle patient population we decided to take a closer look at the infant patients.

So as I mentioned, the majority of the events that we saw were related to neuropsychiatric events, and there were 12 deaths out of the 42 cases. These deaths were discussed and included in the pediatric death case review at large. We did not detect a pattern, as deaths were due to comorbidities in the clinically ill patient population. And some of the comorbidities included TB, renal disease, and again, influenza encephalopathy.

We did have two cases in which oseltamivir was used for prophylaxis, and I'll discuss those two cases. The first case if from the United States in a 25-day-old who had signs and symptom of possible sepsis which started the day before he was initiated on oseltamivir. Four hours after receiving a dose he had a generalized tonic-clonic seizure lasting four minutes, and

required ventilation for apnea. The seizure resolved spontaneously without anticonvulsant therapy, and this particular patient was exposed to a family member with influenza, which is why he was prescribed oseltamivir.

The second case is from France, and this patient was exposed via maternal exposure, and this was a 5-day-old who started oseltamivir on day one, and experienced weight loss due to diarrhea, and experienced jaundice. He was treated successfully with phototherapy and event's resolved.

So, in summary, we did not identify any new unlabeled events. Of note, a review of the neuropsychiatric events by country of origin inform us based on involving terms of reporting neuropsychiatric events. There may be less geographic specificity than was previously identified in the 2007 review. At this time OSE and OND are involved in discussions regarding the possible removal of the phrase "mostly in Japan" from the label. This summarized that the fatalities are consistent with influenza disease progression and complications of comorbidities.

And finally, a review of adverse events in the infant population identified that those events are similar to the pediatric at large. Therefore, we would recommend returning to routine pharmacovigilance surveillance with oseltamivir in the pediatric patient population. Does the committee concur?

I would like to acknowledge many individuals for their contribution to this review and expertise in this Division of Antiviral Products; my own division, Pharmacovigilance, Office of Pediatric and Therapeutics, and the Division of Epidemiology. Thank you.

CHAIRMAN ROSENTHAL: Thank you, Dr. Gada. Before we address your question, let's take some time to ask questions to the prior two speakers as well as Dr. Gada. Dr. Motil? Actually Doctors Greene and Taylor, if you don't mind making yourselves available to a microphone, that would be good. Dr. Motil.

DR. MOTIL: My question, specifically, is directed to Dr. Greene. In your presentation, particularly of the neuropsychiatric events, and with particular interest of the age groups that were so heavily directed in the Japanese analyses, do we have any understanding of the variable substance abuse, substance use in your data analysis? Was that ever evaluated?

DR. GREENE: I'm just bringing up the slide. So we -- so this is exclusively automated electronic data, and the only drug information that we collected for our supplemental influenza surveillance was influenza antiviral drugs, so unfortunately, we have no other information on these other relevant exposures.

CHAIRMAN ROSENTHAL: Dr. Rakowsky? Dr. Rakowsky?

DR. RAKOWSKY: Oh, thank you to all three presenters. Very nicely done. The question for Dr. Greene. You pulled from four sites that might have a large Asian population from the West Coast. Did you break down the adverse events by nationality? I guess what I'm driving at, is there a potential pharmacokinetic predilection among the Asian populations to metabolize this drug differently, and did that kind of come out in your sub-analysis?

DR. GREENE: It's an interesting question. So we actually don't have good race/ethnicity data in our automated electronic claims database, so we did not. But we did observe no association so I'm not sure how much a subgroup analysis we would want to do in the absence of any elevated risk.

CHAIRMAN ROSENTHAL: Dr. Joad?

DR. JOAD: Yeah, I have a question probably to Dr. Gada -- I have two questions to Dr. Gada. The first one is does the drug cross the blood/vein barrier? The pharmaco...

Dr. Lewis: I'll take that question. I'm Linda Lewis, again, I'm with the Division of Antiviral Products. We actually have data that was applied several years ago and was discussed at the 2007 Pediatric Advisory Committee. ROSH [spelled phonetically] conducted a study where they looked at levels of Tamiflu in the central spinal fluid, and they did not find measurable levels in the small samples of volunteers that they

studied.

There was another question about differences in pharmacokinetics between Asian and Caucasian individuals. We have some limited data. Clearly, the Japanese do pharmacokinetics in the Japanese population, and as best we can tell, there is no difference in pharmacokinetics, and the Japanese have not recommended a different dosing in the Asian population. So either with the consideration that Americans are generally larger, sometimes significantly larger, than the Asian population there is no difference in dosing in the two populations.

CHAIRMAN ROSENTHAL: And Dr. Joad did you have a second --

DR. JOAD: My second question to Dr. Gada was when you'd say that your review of a case showed that it was consistent with influenza encephalopathy rather than the drug, what were you using your -- I mean, my understanding was that those are totally compounded. Is there a way that you were separating out which one it was?

DR. GADA: That was basically reported attribution, so the influenza encephalopathy, and they either stated that the encephalopathy was not related to oseltamivir, but they stated that it was related to the influenza disease itself. Out of those cases, 11 of those cases had some sort of attribution.

CHAIRMAN ROSENTHAL: Dr. White?

DR. WHITE: Thank you all. I'm the newcomer here so I'm not aware of the previous discussions that you guys may have had. It seems to me that we're chasing after basically reports from Japan suggesting that this drug has adverse effects in a certain population. Do we have access to the data that they used other than to say some kids did some strange things? Can we actually analyze the data that led them to recommend not using this other than to say it's a bad thing in 19-year-olds?

Dr. MURPHY: Obviously, you can correct me, but I think we get the same reports right? That the Japanese send into ROSH, and get the same --

DR. HAUSMAN: Virtually all of them are the same, and they're subject to the same limitations that ours are. Some of them are extensively well-described case reports and case series, and some of them are not as well-described. So have we put that data through the same statistical analysis that we typically do for our data to find out if there's truly an association, or is this causality, or just association.

DR. MURPHY: Let me just take a shot at. We didn't bombard this committee with all of the reviews from the past. We tried -- Dr. Lewis tried to summarize those in hers, because, the answer is yes, in that we've subjected them to -- two or one day-- complete review -- one day -- of all the adverse events

that we had, and trying to get at this issue of causality, because it's noted there's a difference between association and causality.

And we've looked at pharmacokinetics. We've actually tried to rule out and get a prophylaxis study. We've requested that, and tried to get that done. We looked at other drugs. We presented that data previously, and again, I think Linda, if you want to say something about your summary that you've tried to -- again, you wouldn't have another binder?

DR. WHITE: I'm aware. That's the reason I'm asking just for a summary here. Did you come to the conclusion that there's a difference in the use of this drug? No, that's not correct. Have you determined that there is a reason in the Japanese data that they are worried about this drug that we can't uncover in our population? I guess, is that saying it correctly?

DR. LEWIS: The Japanese data is very mixed. What we get from the company through their Japanese affiliate are the adverse event reports that are sent to the company. We actually invited a member of the Japanese Ministry of Health to come to the 2007 advisory committee, and he made a presentation about their data which is more extensive than what we're able to receive from the pharmaceutical company.

The Japanese are as confounded about this as we are.

They have their mixed data, but they do have a more active surveillance system than the U.S. And so they have some data that compares prospective surveillance reporting of events with or without Tamiflu, and they saw similar events in patients who had not received antivirals, and they saw similar events in patients who received Zanamivir, which is an orally-inhaled product that has very poor systemic absorption.

So the data are all over the place from any kind of surveillance reporting, and more recently the Japanese have reported episodes of what they call transient delirium in patients with influenza that I've been able to find in searching some of the international literature. But it's very difficult even for the Japanese to determine whether this has been a directly causal event, or some inherent process of influenza. I believe Dr. Uyeki has actually worked with the Japanese Ministry of Health to look at some of this data. I don't know if he's willing to speak to that.

DR. MURPHY: And just before we have him speak to that, we have also worked with the Japanese Ministry of Health, and we know that they've had a number of meetings, and they just had an advisory committee meeting on this, and they actually provided reports to us. I think they're where everybody else is at this point, is that they can't make a direct link.

DR. WHITE: It strikes me that may be up against

something similar to what we see in Kawasaki's disease where there is an inflammatory response to the flu in the Oriental population that may be different than what we see in the United States, and that this particular drug may unmask that difference or may confounded by that difference. I mean Kawasaki's Disease -- Jeff, I don't know if you agree or not -- but I think Kawasaki's in the U.S. population, or the typical U.S. population, and the population that's seen in Japan seem to have very different consequences and a different course. And that may be exactly what we're seeing here with the flu, and it's confounded by the use of this drug in different populations.

DR. MURPHY: I'm glad you brought that up, because I asked Dr. Uyeki to address that, because there were a couple of things we didn't go over that are different about the Japanese, and that you know their rate of encephalitis or severe necrotizing encephalitis, and he mentioned it earlier they're ready to access the medicine. I mean, if you think a child is exposed to influenza, and they have a different health care delivery system, and the most use in the world, in the world is driven by Japan's use of oseltamivir.

So they have a very different approach to it, because of this risk concern about encephalitis, but that's my understanding from having listened to their presentations over the past couple of years, and could you add anything to that

please?

DR. UYEKI: I'm sure. So just to clarify, so, you know, I've been interested in this topic, particularly of influenza associated-encephalopathy for more than a decade, and I have hosted the chair of the Japanese Scientific Research Committee on this topic at CDC, and I've visited him in Japan earlier this year. I also met with the U.S. CDC sort of counterpart at the National Institute of Infectious Disease in Tokyo, and went over some of their unpublished data. I cannot and should not speak on behalf of their data. It's, you know, unpublished, and their looking at -- but here's what I could say is that, you know, as Dr. Murphy mentioned, for many, many years Japan has utilized much, much more oseltamivir. Probably about 80 percent of the world's oseltamivir use was in Japan prior to the pandemic.

And so you have a lot of kids who are covered by national health insurance, early access to care, being treated. There's not a lot of untreated kids. They also have really good surveillance, but nevertheless the onset of a number of these symptoms, including encephalopathy, precedes treatment. So some of this is very fulminant, it's same day of illness onset, or the next day prior to receiving treatment. So I think that it's difficult to ascertain what may be attributable to the influenza disease, the illness itself, as opposed to, you know, a drug

effect.

So that's the causality issue. I think it's pretty clear cut when the onset of neuropsychiatric symptoms, however mild to very severe, precedes antiviral treatment. To me, that's the just disease; the influenza illness is triggering that. I would also say that although they've used a tremendous amount of oseltamivir, that is decreasing now, because have other neuraminidase inhibitors that are approved in Japan, and are being used that are not approved here.

So Dr. Lewis mentioned that they're using inhaled Zanamivir in older kids, and that is approved here. They're also using in older kids Laninamivir, which is not approved in the U.S. It's also an inhaler neuraminidase inhibitor. Both Laninamivir and Xanamivir are not really well-absorbed at all. So it's -- you know, if you have encephalopathy occurring after treatment, those drugs, in my opinion, it's pretty unlikely that, you know, it's associated in that they were treated with it, but it's likely that the disease is triggering the inflammatory, affecting those.

And so there's also Peramivir that's being used. It is approved in Japan intravenous neuraminidase inhibitor that is not approved here. That is being used in hospitalized children there. So the relative amount of oseltamivir use is maybe slightly going down as other neuraminidase inhibitors are being

used.

So I think the only thing I can share, again, it's not really fair to say other than general comments, because it's their data, but they've been conducting surveillance for especially more severe abnormal behavior with influenza. And so they've looked at children who only received acetaminophen, children who received only oseltamivir, children who receive acetaminophen plus oseltamivir, children who received Zanamivir, children who received Zanamivir plus acetaminophen, and then more recently children who received Laninamivir. And basically, these abnormal events are occurring across the board in all these groups, again, including, and just the population getting acetaminophen. Now I haven't seen their detailed analysis of this, but crudely, I would say that suggests to me that it's more likely it's associated with the disease, but it's, influenza disease, but I think it's, you know, difficult to sort this out. Thanks.

DR. WHITE: Thank you for answering my questions.

CHAIRMAN ROSENTHAL: Dr. Hudak and then Dr. Motil.

DR. HUDAK: Thank you. I was going to ask a question about the prophylaxis usage of this drug. I think Dr. Murphy may have answered the question directly, but it seems to me I haven't seen any data in presentations about how much of the use in this country has been for prophylaxis versus treatment. But

it certainly begs the question of, you know, do we have any monitoring of events in children who've received prophylactic treatment. I thought there were two deaths reported in this group, but they were clearly unrelated to the drug.

CHAIRMAN ROSENTHAL: May I ask for colleagues along my left to please just introduce yourself into the mic just so that we know who's speaking for the record.

DR. BORDERS-HEMPHILL: My name is Vicky Borders-Hemphill. I'm a drug use analyst in the OSE. And we did not break out the data in term of prophylaxis versus treatment for the national utilization data. In term of the adverse events, another one of my colleagues is going to have to speak to that.

DR. HAUSMAN: My name is Ethan Hausman. One additional comment is that when we go into our drug use analysis we don't -- while we get adverse events from other reporting countries, our drug use databases don't actually systematically incorporate foreign drug use sources, correct?

DR. GREENE: This is Sharon. I have some data on the relative percentage of oseltamivir in the U.S., that's treatment versus prophylaxis. So this is from a paper that's in press, influenza and other respiratory viruses. So in the vaccine safety data link population, 60 percent of the dispensings were for treatment purposes to people who had a clinic visit. An additional 20 percent ostensibly looked like a treatment course,

so it had the right number of day [spelled phonetically] supply and number of units, but they did not have a clinic visit. So if you add those together, that's 80 percent. Only 8 percent were for prophylaxis, and an additional 12 percent, it was not clear from the number of dates supplied, or the number of units dispensed, what the intended -- the intention of the prescription was.

CHAIRMAN ROSENTHAL: Thank you, Dr. Greene. Dr. Motil?

DR. MOTIL: I'd like to go back to the Japanese issue one more time. It's my understanding that the population density in Japan is so much greater relative to population density in the U.S., including, I suppose, in some of our larger cities, and I wonder whether the adverse events, including the neuropsychiatric events, are related, in part, to the population density and risk of exposure living in close proximity.

DR. LEWIS: I don't think we have any way to assess that, Dr. Motil. What you say is correct: The Japanese have very high population density, particularly in the urban centers, but we don't have a way to assess those types of factors. I don't know if the Japanese have tried to do that or not.

CHAIRMAN ROSENTHAL: Dr. Wagener.

DR. WAGENER: So as we begin to approach or come back to the FDA question about whether or not to go with routine

monitoring, I had sort of two quick questions. One is in the under 1-year-olds, do we know the kinetics?

DR. LEWIS: We were able to review from pharmokinetic data as part of an ongoing NIH collaborative anti-viral study group, study that was in progress at the time the 2009 pandemic erupted. In discussions with the NIH and Roche Pharmaceuticals we were able to get that raw data and that's how we constructed preliminary dosing recommendations for this age group, during the time that the emergency use authorization was in progress.

So, we've seen that data. The NIH has published that study in – that's what the recommendations were based on -- as of June 2010 then the emergency use authorization was terminated at the end of the pandemic. At this time it is again considered an off label use in that age group, although I believe, and Dr. Uyeki can correct me if this is not correct, the CDC still does have dosing recommendations in that age group for those physicians who feel the need to use it.

DR. UYEKI: So, this is Tim Uyeki from the Influence of Division CDC. The CDC and the ACIP both recommend use of oseltamivir of treatment of influenza in children less than one year of age and I'd also add that the world health organization also recommends the use of oseltamivir for influenza treatment in children less than one year of age.

CHAIRMAN ROSENTHAL: Dr. Hausman, were you going to

add something?

DR. HAUSMAN: Yes, just one quick clarifying question, comment. In defense to the question it says return to, that would actually be that state where we were in several months ago before we started to the give that process for the advisory committee. Perhaps a slightly different way of phrasing the question would of been continue with routine pharmacovigilance monitoring.

DR. WAGENER: So, let me finish up with --

DR. HAUSMAN: Yes.

DR. WAGENER: Can you tell me, do you know, is the company planning on submitting information to extend their approval for children under one?

DR. LEWIS: We certainly hope so but I can’t comment beyond that.

DR. WAGENER: And then the final part of this is, in looking at routine monitoring is there a way that the under one year old can be separated out?

MALE SPEAKER: No, it’s because you'd have routine monitoring for the drug in general but have a more selective monitoring for the under one year old. The reason I bring that up is it is a drug that is not approved for that group. But clearly based on ELA and the current recommendations from these other organizations; it’s going to be used most likely fairly

extensively, and we know that over a third of all this drug is being used in pediatrics already.

DR. HAUSMAN: Well, when we engage in our routine pharmacovigilance it is not that -- well, I'll say what it is. There are certain issues that come up to the safety reviewers like Dr. Gada and they periodically go back do second looks which may be very brief or sometimes very comprehensive for particular issues that you don't necessarily rise to the level of performing an in-depth consult review, before them assessment is actually done. So, when we go back it's likely that there are things that will continue to look at, like the under one patient population. And if we do end up seeing anything it may rise to the level of actual insist in taking the comprehensive review. So, just because we're not making any particular recommendation now doesn't mean it's totally on the back-burner and off the radar screen.

DR. MURPHY: So, Nathan I guess that question is --

DR. HAUSMAN: Ethan.

DR. MURPHY: Yeah, Ethan, sorry -- is that you could make part of your routine know-- I think this is the question -- to look at the -- to breakdown that -- not just have pediatrics but to breakdown under one like you've done.

DR. GADA: Yeah, we can certainly break down by age but part of our routine surveillance would be monitoring all

adverse events for oseltamivir, including in the pediatric population, which would also include the infant patient population. So, it is part of the routine surveillance for of oseltamivir monitoring.

DR. WAGENER: My worry is that if we wait for something to raise our concern in the under one year old it may be a long time, because of just the practice pattern that people are, sort of, going to be using it more but they are going to assume that it's safe and effective.

CHAIRMAN ROSENTHAL: Drs. Towbin, Santana, and LaRussa.

DR. TOWBIN: Well, I guess I have two comments and one question. So, one comment is I'm quite impressed by Dr. Greene's presentation and one of the things that I noticed was how we've lumped so many things into these neuropsychiatric effects. The most common diagnoses were things like depressive disorder, not otherwise specified, or anxiety disorder, not otherwise specified. Which really are a syndrome of symptoms, you know, a day late and a dollar short of meeting full criteria for anything. And I think that we really don't have a good sense of what the base rate is for these kinds of symptoms in the population that's studied. So, I feel a little bit of caution about that, you know, the more severe manifestations things like delirium and hallucinations may be a different

story. But I was just impressed with how many of those accounts were for what would be symptom based experienced of anxiety or low mood or decreased interest in mutual activities. And I think that has to be taken with a grain of salt.

A second comment is that since the prescribing pattern for this so often falls in pediatrics but outside pediatrics, I'm curious about what the dosing recommendations under one year olds are and how readily available those are for people. Because if we're going to go the direction of people beginning to use this in the guidelines by the World Health Organization and others, one would want those dosing recommendations very available to people. And if it isn't going to be in the package insert, how that gets out there is going to be very important.

DR. LEWIS: Well they are, as I said, posted on the CDC website and have been since the time of the pandemic. During the pandemic, when we had the emergency use authorization, they were also posted on the FDA website, but at the termination of the pandemic those were taken down. But they remain on the CDC website.

DR. UYEKI: And they're also in the American Academy of Pediatrics website through the annual AAP recommendations.

DR. TOWBIN: So, one thing we might consider is whether at some point that would find their way into the regular package insert or anything and I know that the industry has to,

kind of, push for that. That is not a thing that you guys can do but to the degree that they might be disinclined to make changes in the labeling, maybe there can be some encouragement for that.

DR. LEWIS: As I said, we hope to get those into the package insert.

DR. TOWBIN: And then one last comment if I can, this doesn't change the subject too much, but in the briefing materials there were some comments about two T-Interval studies with also oseltamivir. And I believe that there was a comment that the study that had been done in 2000 lacked a positive control group and there was still some question about that. So, I was just wondering if we've seen a study that's been produced that's resolved those questions to everyone's satisfaction. I didn't see anything in the briefing materials about that.

DR. MARCUS: There was a study conducted in 2000 that lacked a positive control -- I'm sorry?

CHAIRMAN ROSENTHAL: Can you just tell us your name?

DR. MARCUS: I'm Kendall Marcus. I'm the deputy director for safety in the Division of Anti-virals

CHAIRMAN ROSENTHAL: Thank you.

DR. MARCUS: There was a study done in 2000 that lacked a positive control. Positive controls are really recommended as part of routine thorough QT studies around 2005

when ICH guidelines about conduct of studies were issued. The study was well conducted in all other respects and doses up to seven that achieved exposures up to seven-fold the marketed dose were achieved, without any evidence of prolongation of the QT interval.

Now the lack of a positive control really does not, I think in our minds, substantially minimize the finding of no QT prolongation. Positive controls are usually used as a measure of determining the population's susceptibility to QT prolongation and in clinical, thorough QT studies where positive control has become important are situations where the positive control, which is almost exclusively Moxifloxacin, either prolongs the QT interval greater than it is expected or less than expected, such that, the point estimate and then the confidence intervals around the point estimates of QT prolongation for the test drug can't be ascertained with confidence.

So, in a situation where you've got seven-fold the exposure of the marketed dose, I think that there is a high degree of confidence that the study is negative. Now with regards to a view of that by a QT IRT group, they recommend that another thorough QT study be done if the sponsor wishes to make a negative claim. That's a bit different than having a concern that the drug prolonged the QT interval.

So, you know at this time we don't have any compelling reason to ask the sponsor to conduct another thorough QT study with a positive control. Now that's not to say that that won't be done at some time in the future, and I hope that addresses your question.

CHAIRMAN ROSENTHAL: Thank you, Dr. Marcus. Dr. Santana.

DR. SANTANA: So the question before us is if we endorse the recommendation that we continue the present surveillance and monitoring time for this agent. My question to the agency is because of the use of this agent for treatment prophylaxis is very dependent on epidemics and things like that it's not expected to be too stable, over time it may change abruptly. In addition to coming to this committee to request that there be a change in the surveillance and monitoring plan what other regulatory tools does the agency have outside of us in order to enhance or change that plan and it needed to be done in a very short period of time?

CHAIRMAN ROSENTHAL: Dr. Hausman, were you going to?

DR. LEWIS: Well, we actually have very close communications between the review division and the Office of Surveillance and Epidemiology. And we've been looking at this for so many years now I think it's unlikely that we would stop looking at it completely Dr. Gada is very good at pointing out

individual case reports to us that she thinks warrant additional investigation, and trying to get follow up information for some of them. So, you know, our routine is if anything looks unusual we go to enhanced surveillance during influenza season noting that there is always a lag between the time of drug use and the time of reporting of adverse events, but that's been our method of looking at this over the last many years.

CHAIRMAN ROSENTHAL: Dr. Hausman, you had something to add?

DR. HAUSMAN: Yeah, It's just the way the drug portfolio modeling goes. The way the safety evaluators work it's very much in since with theirs, they are very, very good at picking up very rare string signals that just pop out at you. So some of the new ones are the more common things that were already reporting in the label, that still continues, but the advantage of routine portfolio monitoring with safety evaluators like Dr. Gada is they pick up on those really rare things really fast and that's when the red flag goes up as an agency internally detected issue.

CHAIRMAN ROSENTHAL: Dr. LaRussa, you're up and Dr. White you're on deck.

DR. LARUSSA: So, just quick related question and I apologize, I don't know this, but what's going to stop happening that's happening now when you go the routine surveillance?

DR. GADA: Sorry, what's going to stop when we go to routine surveillance?

DR. LARUSSA: Yeah, you want to go back to routine surveillance. So, it implies that you are not going to be doing some things that you are doing now and I just wanted to hear what you're not going to be doing.

DR. GADA: During the 2009 pandemic year and then entering the season following that we conducted bimonthly safety reviews and have numerous discussions within the agency including with the division of anti-viral products and conducted summary reports from the Division of Pharmacovigilance and Division of Medication Error Prevention, the Division of Drug Use and so that was what more of an enhanced pharmacovigilance surveillance, and routine surveillance include monitoring the reports that we see, the adverse event reporting we see for Tamiflu and would not necessary include bimonthly reports.

DR. MURPHY: I think really what happened when we asked for this recommendation, it means that there is nothing that the committee needs continuing review about. That there is not particular that we need to bring it back because this product is most unusual. I think it spins the community more than any other product and probably because of the inability to come to any conclusion. So, if we say return to routine, then as you saw on the slide, the committees asked for follow ups

many years in a row. That would mean that that would not happen.

CHAIRMAN ROSENTHAL: May I add something to that, unless some new signal comes up. So -- and disregarding how the committee tends to work it’s much easier to ask for enhanced monitoring or additional things than it is to actually drop back to routine monitoring because people are nervous about this sort loss of ascertainment or loss of identification of something important. But the routine system is very good at picking up even, you know, quite rare blips on the adverse event reporting. Yes.

DR. GADA: I just want to point out that for this past flu season you didn't continue or start to go back to routine pharmacovigilance and didn't have an enhanced monitoring and didn't identify any regarding [inaudible] during this past season.

CHAIRMAN ROSENTHAL: Dr. White, thank you for your patience.

DR. WHITE: I’m sorry, I just wanted to respond to Dr. Towbin’s concern about a lack of positive controls. The clinical expression of long QT is sudden death and torsade. And I would think that if this drug had a significant effect with the number of uses and the amount of uses had over the years, we would of had some reports if torsade or sudden death related to

cardiac and the six sudden deaths that were recorded myocardosis is not a manifestation of long QT nor is respiratory arrest with heart congestion -- so, I think whether we have the positive control or not we've done the clinical control. Which is, it doesn't seem to be a problem in this population. Is that fair?

DR. TOWBIN: I think so. One comment back is that since the risk may be elevated in those with cardiovascular disease I wasn't sure whether the was some additional study that might be needed since that population would also be one at risk for further cardiac involvement and are subsequent to infection.

DR. WHITE: Probably the children with cardiovascular disease are using this drug more frequently and more commonly and if it were a risk I think it would have shown up in outer reports. I mean, do we have report of torsade or sudden cardiac death in these patients that we can cite?

DR. LEWIS: A few years ago, and I think I included a little bit about this in the background document for the committee, but recognizing how much you guys have to review, there was a case report of prolonged QT and torsades in the patient who was receiving oseltamivir in combination with sotalol which is well described --

DR. WHITE: Right, sotalol is sort of a known --

DR. LEWIS: So, that is what triggered out initial re-look at the QT issue and we are not able to identify any

specific signal in going back through our errors database at that time

DR. WHITE: Thank you.

DR. TOWBIN: And just a comment on that, if I may -- this is Dr. Towbin. So I think what drew my attention to this is on Page 6 of the safety review where there were 11 cases I torsade in patients exposed to oseltamivir between 2000 and 2009. Most reports involve patients with concomitant cardiac disease or concomitant medications known to prolong the QT-Interval while the review was not entirely conclusive regarding these concerns it is recommended that a thorough QT study be performed to assess the potential risk of QT prolongation associated with oseltamivir.

CHAIRMAN ROSENTHAL: Thank you. Doctors Gada or Marcus, it looked like each of you is leaning towards your mic. I want to give you a chance to speak if, no, you’re not? Okay. All right. Dr. Wagener, you had a question?

DR. WAGENER: I apologize for not remembering which one of the speakers mentioned this, but during the EUA the company was asked to do some type of monitoring for the under one-year-old. Were there any results related to that and is that monitoring continuing?

DR. LEWIS: During the pandemic the company was asked to provide monthly safety updates to the FDA from their global

pharmacovigilance network. That did terminate at the end of the pandemic. So, no, they are not still doing that. We received all of those reports into our AERS database. So, you saw on the slides there was a big spike in international case reports during the pandemic period and that's where a lot of that came from.

So, we had those reports. That's what included in the AERS review for the under one-year-olds and we did not see anything different in that age group compared to the approved age group.

CHAIRMAN ROSENTHAL: Okay. Other questions? Yes? Yes, Dr. Wiefling?

DR. WIEFLING: So, this is not so much about the scientific basis of cancer, but more the general message for the public or for the parents, and I just want to make sure that I have this right, and maybe it's not, but that's what I'm putting out there, but after all of today's presentations is it safe to say that the information that we've seen today really emphasizes that immunizations are important and we may not be doing quite as good of a job as we need to doing in immunizing our children against that and the safety profile of Tamiflu as we're determining it seems to be safer than the disease mortality itself for children. And so, is it an opportunity to sort of get that message out there in some way? Is this is a platform

for saying immunizations are really important? This is not just a cold. Children do die from the flu. If you don't have your child immunized Tamiflu is an opportunity to salvage that given the safety profile that we've determined today.

DR. LEWIS: I do think that we would fully endorse a better immunization program because clearly influenza causes deaths every year in the pediatric population that are preventable. We may not be able to prevent all of them even with a perfect immunization program, but we could prevent an awful lot of them as Dr. Uyeki said earlier.

DR. MURPHY: I think you got the message we were trying to outline for the committee by having, you know, the experts that come and tell everybody that this is a serious disease and kids will die every year and more than should as far as we can see. And some of the are going to die quickly, so I think that, you know, some of these questions about well, it would be great if we could find out better scientific information about what kids are going to be predisposed or is there some way that you could identify that, you know, with these future investigations, but I think clearly those two messages are part of what we think should be coming out of this.

CHAIRMAN ROSENTHAL: Thank you for that comment. That is an important public health comment. Other comments or other ideas before we move on to the vote? All right. Let's bring up

that slide again just because we always do that from Dr. Gada's talk. And our representatives from industry and from health care organizations will not be participating in our vote today, but others will.

DR. MURPHY: Could I just say one thing, Jeff?

CHAIRMAN ROSENTHAL: Yes.

DR. MURPHY: Just before we take the vote that, you know, I just want to make sure the committee understands that I think everyone here has heard them very clearly as far as the concern for the under one-year-old and the ongoing increased use and that, you know, if the Office of Surveillance and EPI sees anything they'll notify the division and us and we'll discuss it and decide if we need to bring it back. I mean, I just want to lay that out on the table. Routine monitoring doesn't mean that you never get any follow up if we think that there is something that needs to be looked at in the under one-year-olds. So, did you want to add to that?

DR. HAUSMAN: Yeah. The comment would be that routine monitoring is actually a very robust and a very active process.

CHAIRMAN ROSENTHAL: Other comments or questions before we -- all right. So, the question before us is does the committee support a recommendation to the agency to return or continue routine pharmacovigilance surveillance for oseltamivir; and the way that we'll do this is a show of hands and then we'll

go around the table and let everyone know our votes. So, all in favor of returning to routine pharmacovigilance surveillance for oseltamivir? All right. And opposed? I see no hands opposed. Dr. White, can you start us on the vote?

DR. WHITE: Thank you for the presentation. It clearly outlined the concerns. I voted because I don't think you've uncovered any unusual aspects, but I would encourage the industry to submit an application for supporting the use of this drug under one-year of age, which is a highly vulnerable population.

DR. MOTIL: Dr. Motil, I vote yes to return to routine monitoring.

DR. HEWITT: Geri Hewitt, I vote yes to return to routine monitoring.

DR. WIEFLING: Bridgette Wiefling, I vote yes to routine monitoring.

DR. MINK: Jon Mink, I vote yes.

DR. GLASIER: Charles Glasier, vote yes.

DR. LARUSSA: Phil LaRussa, vote yes.

DR. RAIMER: Sharon Raimer, yes.

MS. CELENTO: Amy Celento, yes.

DR. JOAD: Jesse Joad, yes.

DR. KRISCHER: Jeff Krischer, yes.

DR. TOWBIN: Kenneth Towbin, yes.

DR. WAGENER: Jeff Wagener, yes, and I compliment the agency on a superb presentation.

DR. RAKOWSKY: Alex Rakowsky, yes, and again compliments and also compliments of Dr. Uyeki. Thank you for your presentations.

DR. SANTANA: Victor Santana, and I vote yes.

DR. REED: Michael Reed, I vote yes.

CHAIRMAN ROSENTHAL: All right. Thank you very much for that. Now, in a few minutes we're going to move into the open public session. Before we do that, just a couple of housekeeping points, the Pediatric Advisory Committee has asked the agency in the past for access to unredacted briefing information. The agency has given us a disc with a thumbprint, with your fingerprint, on the CD. That disk has unredacted information. Please return these discs to Walt during the meeting or at the conclusion of the meeting.

The other thing I'd say about the unredacted content is if you, or your administrative assistant, has loaded them onto your computer please delete that from your computer. I just deleted it from mine and because that information is strictly, strictly confidential.

The other thing about the unredacted information is that it's best to not look at it unless you need to. So often we are able to perform a sufficient review of the issues looking

at the redacted versions and that's the safest version to refer to. During the discussion none of the information that's in the unredacted CD should be brought to discussion because that again is strictly confidential.

So, Walt will accept CDs whenever you have them and yes, Dr. Mink?

DR. MINK: This applies both to the unredacted and the redacted information. Is there any way this can be provided in a way other than .pdf's embedded in a Word document? Particularly for those of us who don't use PCs it's impossible to open them and adds about an hour to our time to try to extract them.

CHAIRMAN ROSENTHAL: This is one of three volumes that you can receive on your doorstep. Now, having toted these on planes, trains and cars to come to these meetings, the electronic version seems much more friendly.

DR. MINK: I'm not at all opposed to an electronic version. It's just that embedded .pdf for Word, which -- Word version of the software will not allow us to open it.

DR. MURPHY: The answer is yes.

[laughter]

CHAIRMAN ROSENTHAL: You're asking about alternate electronic formats? Yes.

DR. MURHPY: I mean, and I wouldn't suffer for hours

if you're having trouble. Just let us know because Pam was able to, I hope, fix it for you. Did I get the correct information?

MS. WEINEL: I did when I was notified.

DR. MURPHY: Yes, when was notified. So, if you're having trouble, please do not spend hours trying to go through it. I think our Windows is still at 2003 or --

MS. WEINEL: I think we're up to seven.

DR. MURPHY: You are, we're not. [laughs] So, when sometimes you're dealing with older systems themselves. But, we will try to get you a version that is much easier as soon as possible.

CHAIRMAN ROSENTHAL: Dr. LaRussa and Dr. Joad each have a comment about this as well.

DR. LARUSSA: Just a quick comment, if you use a PC simulation program.

DR. MINK: Yeah, then you have to buy the PC version of Office and have to have the correct older version and -- it can be done, but it's not easy.

CHAIRMAN ROSENTHAL: All right. Well, we'll work through these technological issues, Dr. Joad. I'm noticing that everybody who has a question or a comment seems to have an Apple computer in front of them.

[laughter]

I can see how that's a problem. All right. Yes, Dr.

Joad?

DR. JOAD: Well, I'll give a testimony that I did have that problem and it was fixed. Thank you very much -- on an Apple.

CHAIRMAN ROSENTHAL: Okay. All right. Other comments? Walter, do you have any other short housekeeping issues before we move on to the open public forum? All right.

OPEN PUBLIC HEARING

CHAIRMAN ROSENTHAL: We're going to get started with this a minute early. So, this is the point in our meeting where we are open for public hearing and there's a statement that I read as we being this process.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Pediatric Advisory Committee meeting FDA believes that it is important to understand the context of an individual's presentation. For this reason FDA encourages you, the open public hearing speaker, at the beginning if your written or oral statement to advise the committee of any financial relationship that you may have with any firm or any group, their products, and if known their direct competitors that is likely to be impacted by the topic here addressed in your presentation.

For example, this financial information may include the payment of your travel lodging whether expenses in connection with your attendance of this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial

relationships at the beginning of your statement it will not preclude you from speaking.

Now that having been said, we received no requests to speak or present. We have received one set of comments that are displayed outside and for those of you around the table these comments, these materials can be found in the green folders that were distributed to you.

I'll read a brief letter that introduced these attachments and then I'll just briefly describe these attachments by reading the introductory paragraph of each of the three.

So, on April 30 of this year, Dr. Ellenberg received an email letter that was sent on behalf of Dr. Wesley Burks who is the president of the American Academy of Allergy, Asthma and Immunology and also from Dr. Stanley Fineman who is the president of the American College of Allergy, Asthma and Immunology.

And the letter to Dr. Ellenberg says, "On behalf of the American Academy of Allegy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology, we're submitting our comments for review regarding the upcoming May 7 Pediatric Advisory Committee that will discuss pediatric focus safety reviews as mandated by the Best Pharmaceuticals for Children Act and Pediatric Research Equity Act for Dulera,

Nasonex and Omnaris. We hope you find this information helpful and that you will not hesitate to contact us should you or the advisory committee have any questions" and then that's signed.

And before just reading briefly what these are about I'll just say that the material will all be entered into the materials for this meeting, the docket as it were, for this meeting into the meeting record.

So, for Dulera, it says the attached information is intended to provide pertinent data that will assist the Pediatric Advisory Committee in forming conclusions and making decisions. This information is not intended to advocate for any indication dosage or other claim that is not covered in the package inset. We believe the literature supports the safety in pediatrics for the current indication of Dulera.

And I just read a, you know, one-inch introductory comment and this is a multi-page document, as are the others.

The similar paragraph for Nasonex, the attached information is intended to provide pertinent data that will assist the Pediatric Advisory Committee in forming conclusions and making decisions. This information is not intended to advocate for any indication dosage or other claim that is not covered in the package inset. We believe the literature supports the safety in pediatrics for the current indication of Nasonex.

And similarly for Omnaris nasal spray, the attached information is intended to provide pertinent data that will assist the Pediatric Advisory Committee in forming conclusions and making decisions. This information is not intended to advocate any indication dosage or other claim that is not covered in the package inset. We believe the literature supports the safety in pediatrics for the current indication of Omnaris.

And so, again those documents have been distributed to the committee and will be entered into the meeting record.

All right. And that is going to conclude our open public meeting.

Now, at this point in the schedule, we have time for a lunch break and the schedule has us returning at 1:30 for presentations for Viread and those presentations need to be at 1:30. So, we're going to have a little bit of a longer lunch than usual. So, enjoy yourselves.

Let me remind you, please do not talk about any of the topics that we're discussing in the meeting while you're off enjoying your extended lunch.

DR. MURPHY: I mean, I would get back -- I'd kind of aim for 1:15, that way we really get started on time, but the rest of the divisions have been told to be here at 1:30. So, if you guys could aim for between around 1:15, then if they're here

we can get started. We should be able to get started.

CHAIRMAN ROSENTHAL: And as we're breaking I just want to thank the presenters again from this morning. I think the information that you presented really helped us through quite a robust discussion and thank you.

VIREAD (TENOFOVIR DISOPROXIL FAMARATE)

STANDARD REVIEW OF ADVERSE EVENTS

CHAIRMAN ROSENTHAL: All right, well, let's -- as we get seated, get ready to get started for the afternoon session. We welcome everyone back. Hope everyone had a nice lunch. Did everybody get -- did anybody not get lunch? Did anybody get a nap?

[laughter]

CHAIRMAN ROSENTHAL: Okay. A walk. Okay, good, good, good. All right.

Well, we are about to start with the first agent of the afternoon, Viread and Dr. Nadia Hejazi will be presenting a standard review of adverse events for us. Dr. Hejazi is a pediatric neurologist. She received her medical degree from King Abdulaziz University in Jeddah, Saudi Arabia. Dr. Hejazi received additional training in neuropathology and pediatric EEG at the University of Washington in Seattle and also at UT Southwestern in Dallas. She was a research fellow in cellular electrophysiology at the National Institutes of Health. She studied the roles of the glycine receptor in something.

DR. HEJAZI: Hypoglycemia.

[laughter]

CHAIRMAN ROSENTHAL: And these studies led to the

discovery that the glycine receptor played a previously unrecognized role in response to cannabinoid drugs. So Dr. Santana, I'll just point out, for the afternoon session, there are a few different recusals. We'll try and keep track of them. Those who need to be recused, I think know who you are, so if Walt and I slip, then please help us out but we'll try and remind people as we go along. So Dr. Santana is not sitting at the table for the discussion of Viread. So Dr. Hejazi.

DR. HEJAZI: Thank you. Good afternoon, everybody. I'm going to present Viread safety review this afternoon, and so they are clients and you might be not familiar with them so I'm not going to go through them. Viread is a nucleoside, and you know HIV and HPV reverse transcriptase inhibitor that is indicated for the treatment of HIV and Hepatitis B infection in adults. Viread has been approved in children for the treatment of HIV infection in children 12 years and above, and this approval was in March 24, 2010. And this safety review was triggered by labeling change which was done under both PREA and BPCA, as result of these studies.

Viread has been recently approved in children 2 to 12 years of age, and this approval was in January of 2012. And this approval will trigger another safety review at the end of the year. Viread is marketed by Gilead Sciences as oral tablet and oral powder, and both oral tablet and oral powder are based

on body weight. Those both are based upon body weight. Tenofovir is available in other formulations, and only Truvada is approved in children 12 years and older, and only Complera and Atripla are approved in adults. While Lamivudine and Tenofovir FDC tablet combination is not approved in the United States yet, and neither is Lamivudine, Tenofovir, and Nevirapine.

The Asian market approval for Tenofovir Viread was in October 2001, and original request was initially issued in December 2001, and after several amendments was reissued in September 16, 2010. And pediatric exclusivity was granted one year later.

And I would like to mention here that the PREA is preferred for children two years and above. HIV studies for children birth to two years were not conducted, and this was because of safety concerns, and the agency is looking at safety for children 12 years older before deciding whether to conduct studies in birth to less than two years of age.

The PK of Tenofovir review was evaluated in eight children 12 years and above with HIV 1 infection, and who received 300 milligrams. And the exposure in these children match that of the adults receiving the same dose. And the efficacy of tenofovir was conducted in 87 pediatric patients who were undergoing treatment experience 12 to 18 years of age and who were divided into two groups: a placebo group and a

treatment group. However, the study did not show a difference in biological response between the two groups, but the subgroup analysis showed that the lack of neurological response may be attributable to the fact that 90 percent of the subject had an NRTI resistance-associated substitutions in their HIV isolates.

At the end, the efficacy was extrapolated from adult studies that was supported by PK and safety studies in children 12 years and older. So the overall conclusion of the efficacy study is that the FDA recommends the use isolates expected to be sensitive to Viread. Viread has a boxed warning for lactic acidosis and severe hepatomegaly with steatosis, including fatal cases [spelled phonetically], and the warning is for the drug as a class as a whole, the nucleoside analogs including Viread. The boxed warning also includes a caution for hepatitis, B patients who had discontinued with Viread may develop acute exacerbation of their hepatitis, even months after stopping Viread. And the FDA recommends monitoring of hepatic function for several months before resuming treatment.

I'm now going to discuss the relevant safety issues, and as you can see here we have a list of warning and precautions. The most important ones are the bone mineral density of 5.6, the decrease in bone mineral density, and the 5.3 the new onset or worsening renewal impairment. And I'm going to discuss this with more detail.

With regard to decreased bone mineral density, the FDA recommends the assessment of bone mineral density in adults and pediatric patients with a history of pathological fractures and other risks of osteoporosis. And this was based on trials that were conducted in adults and children with HIV that found that Viread can cause decrease in bone mineral density, as early at 28 to 48 weeks of trial. And this reduction was mainly seen in the hip and lumbar spine, and it was sustained through Week 144. Fractures were recorded as well, and the decrease in bone mineral density was accompanied by significant increases in biochemical markers of bone metabolism suggest increased bone turnover. And based on these clinical trials and post marketing reports, the bone effects may be related to proximal renal tubules, or it may be related to direct effects of Viread on osteoblast and osteoclast function.

And because of the seriousness of this adverse event, the FDA under FDAAA required a study to elucidate the mechanism of the tenofovir effect on bones and proximal renal tubules. And this study will be conducted in HBV-infected pediatric patients, which is a study that’s already required under PREA for the HBV indication. This study will basically assess renal function and bone markers and will correlate these parameters with those of bone marrow density for DEXA scan.

And, so, to continue with the safety adverse events, I

will discuss the adverse events that occurred during clinical trials, and these are mainly proximal renal tubulopathy and decreased bone marrow density Z score that was reported in association with Viread use. And this is an important course of events as you will see later when I discuss the adverse event reports. Other events were not different from those occurred in adults and are listed here, and as you can see, through the post marketing experience, where mostly we are admitting adverse events, which is labeled adverse event.

And now we switch gears, and I'm going to talk about drug utilization and, as you can see from this slide, sort of the number of prescriptions that was dispensed from Viread and the commercial product, from Atripla, and Truvada. And as you can see, the pink line -- this is a big year where the prescriptions were increased from 200,000 -- from 300,000 prescriptions in 2002 to 900,000 prescriptions in 2004, and then dropped, and the drop was associated with the increase of prescriptions dispensed for both Truvada and Atripla.

And this slide here show the number of prescriptions that sold and received by patients based on age group, and as you will see in the red font that most prescriptions were sold and were received by patients who are 18 years and older. And, again, here, this slide shows two diagnoses and top prescribing specialty per U.S.-based office physician practice from January

2002 to December 2011, and as you can see the top diagnosis was HIV. And at the top, the top diagnosis was HIV, and the top most-captured age was 18 years and older. And the top prescribing specialties were infectious disease and internal medicine, which made up 56 percent of all prescribing specialties.

And this slide shows the -- I took a number of adverse event reports since the approval of Viread from October of 2001 to January 2012, and as you can see here, this -- the total number of pediatric patients were 427; 418 were serious reports, and this statement -- including 45 deaths, and these reports included duplicate reports. And this included seven deaths where pediatric age was not known.

And as you can see, in this slide, if you recall the 420 serious adverse effects, 415 where age was known. This includes 45 deaths, and seven were pediatric deaths where the age was unknown. The pediatric reports were about 41, and unduplicated pediatric reports were 379, including five deaths. Of the 379, 300 reports were excluded because of transplacental exposure to Tenofovir. This leaves us with 79 pediatric cases, including five deaths.

And so if we have five pediatric deaths, four of them occurred in newborn infants, and these infants were involved in an HIV trial that was conducted outside the U.S. in South

Africa, Cambodia, and Cote d'Ivoire. It was [unintelligible] off-label trial that involved the mother and infants. And the four deaths were -- the four cases were confounded by comorbidities. The first was a newborn who was -- who died possibly of meningitis, and the second was -- newborn was -- had neurological disorders; a neurological disorder and developed laryngomalacia, and died at the age of seven months. And the two remaining cases had gastroenteritis and probably died of sepsis.

And the fifth case was a 17-year-old female who developed -- who died of respiratory diseases mimicking Guillain-Barré syndrome, and she was on a combination of -- HIV drug combination, which is no longer used. And so -- and as I said, this -- you may recall the concomitant -- the concomitant morbidity in these five pediatric deaths, these deaths may be not directly related to Tenofovir toxicity.

And so we now move to discuss the serious non-fatal adverse events associated with Viread, and the [unintelligible] number is 43, and it's not 47. I apologize. We have decreased bone mineral density, six cases, and renal dysfunction, which two -- these two events, unlabeled events, and we have anemia and cardiac events, and bone marrow necrosis, and these three are unlabeled events.

We start with the bone mineral density, and as you

recall from Viread from earlier that Viread can cause decreased bone mineral density, and we have six cases reported here with this adverse event. The first case is a 4-year-old who developed decreased bone mineral density, and which approved after Tenofovir was discontinued. And the second is a 10-year old-male who developed Fanconi syndrome and rickets, and also improved after 2003 was discontinued. The third case was a 12-year-old who also developed Fanconi syndrome, rickets, and hypophosphatemia after starting Truvada and Kaletra, and improved after discontinuation of Truvada.

The fifth case was a 12-year-old who was injured while running and was found to have reduced bone mineral density, and because there was no further progression of bone loss, he was continued on Tenofovir. And then the fifth case was another 12 years old who developed osteomalacia while on Tenofovir and was -- in 2003 was discontinued and vision improved, and also the patient improved while on treatment of K-phosphate and vitamin D. And the last case, a 16-year-old male who developed reduced bone mineral density and rickets, and renal tubular injury after being on Tenofovir 2003 for two years, and there is no reportable outcome.

The second of the serious and non-fatal adverse events is renal dysfunction, and this a labeled adverse event, but because of the potential seriousness of this adverse effect, a

lot of cases were looked at and reviewed to see if there is any unexpected association. And we have three pediatric cases described here. The first is a 10-year-old who was taking concomitant nephrotoxic medications, and the second was a 17-year-old who has shown improvement after Tenofovir was discontinued, but nine months later experienced a renal failure while taking antiretroviral regimen that did not contain Tenofovir. And the third case was a 16-year-old who was -- who developed renal failure while on Tenofovir. And I would like to mention here, the Tenofovir label has guidelines to adjust Tenofovir pills based on clearance, creatinine clearance.

The third of the serious non-fatal adverse effects is anemia, and it remains an unlabeled event. And we have here 15 cases of anemia. Eight of them were due to transplacental exposure to Tenofovir, and the six remaining cases including a 9-year-old who was diagnosed with mycobacterial avium complex infection, and three cases where the patients received concomitant zidovudine, and in this case zidovudine can cause anemia. And, a case of renal failure anemia, which was noted three months after Tenofovir was discontinued.

The fourth of the serious non-fatal adverse effects is cardiac event, and cardiac event is not a labeled event, and we have two cases. An 8-year-old, I’m sorry, an 8-year-old male who developed QT interval prolongation, but in addition, he was

on -- in addition to Tenofovir, he was on other NRTIs which were non-specified. And the second case was a 10-year-old male who had an SBT [spelled phonetically] and also had the Coxsackie virus B6-induced carditis.

And the fourth -- the fifth and the last of the non-serious, non-fatal serious adverse effects is a bone marrow necrosis, and we had one case, a 7-year-old, who developed leukopenia and focal bone marrow necrosis while on a combination of tenofovir and abacavir, and it does say, in addition, the person had hypocellular bone marrow. Leukemia and lymphoma are excluded in this case, and the patient -- the patient's white blood cells recovered after the didanosine dose was -- after the didanosine was discontinued, but not the necrosis of the bone marrow. And, in this case, the didanosine is labeled because advances leukopenia; also, the didanosine is known to cause decrease in CD4 when giving -- in any situation with Tenofovir.

And this concludes the Viread pediatric safety review. Labeling change was in March 2010 to grant an indication for HIV infection, children 12 years or older. No new safety signals were identified. The FDA recommends continued routine monitoring. Does the committee concur?

CHAIRMAN ROSENTHAL: Thank you, Dr. Hejazi.

DR. HEJAZI: Thank you, and I would like to thank all the individuals on this flight [spelled phonetically].

CHAIRMAN ROSENTHAL: Thank you. Questions for Dr. Hejazi? Dr. White?

DR. WHITE: On your one patient with QT interval prolongation, do we have a baseline EKG available, and do we know what the calcium might have been in that patient? Since you have calcium problems noted as a well-described side effect, QT interval prolongation could have been secondary to calcium metabolism.

DR. HEJAZI: I have no -- I don't know if Debbie knows.

DR. BOXWELL: Debbie Boxwell, division of pharmacovigilance, FDA. That particular case provided so little information, there's no way to really assess it. It was a very sparse case.

CHAIRMAN ROSENTHAL: Yes, Dr. Wagener?

DR. WAGENER: I was interested in the anemia cases, which are not included as listed adverse events, and none of the 15 were transplacental. Is there any type of warning in the package as far as transplacental exposures that people should be cautious of?

DR. HEJAZI: Not on the label, no.

DR. WAGENER: Do you have the label?

DR. HEJAZI: I don't think so --

DR. WAGENER: I'm calling up the label.

DR. LEWIS: One comment is all pregnant women who are known to be HIV-positive, whether they're on treatment or identified near the time of delivery, are recommended to receive cydognadine [spelled phonetically] as part of the prophylaxis regimen. So, if we don't have that information specifically spelled out in the case report, we don't have any way to know if they were also receiving cydognadine. And that is well-known to cause anemia, who -- even in the newborns.

CHAIRMAN ROSENTHAL: Other questions? Dr. Motil, please.

DR. MOTIL: I have a couple of comments and one question I'm a bit bothered by the bone mineral density information, in part because the association between this particular certain drug effect -- I think is, it needs a lot more study. One of the issues is that bone mineral density deficits are seen in many chronic illnesses.

And so I guess my question really relates to the issue of what do we know about bone mineral deficits? What do we know about vitamin D status? What do we know about calcium intake? What do we know about all of these other factors that go into bone mineral metabolism in this -- in the context of HIV disease in children? Because I would postulate that probably this particular symptom is found in many of these children independent of, one, drugs, and then two, probably a number of

drugs.

DR. LEWIS: This is a -- sorry, this is Linda Lewis, Division of Antivirals, this is a side effect that has been well described with Tenofovir in both animal toxicology studies and in the adult clinical trials. We have been working with Gilead Sciences to try and elucidate the mechanism of bone mineral density changes in all populations. And it appears that at least some of the BMD loss is due to renal tubulopathy and an increase in phosphate wasted that can lead to an osteomalacia-type picture, but there appears to also be a direct effect on bone mineral density. So, I think there may be some effect on osteoblasts and osteoclasts.

In adult studies, which are certainly larger and more able to tease out some of these issues, there are changes in many of the biochemical markers of bone metabolism that suggest rapid turnover of bone but with a net loss. In the larger adult studies, we see changes in bone mineral density with greater declines in populations getting Tenofovir in comparative trials. Well, yes, there was a small decline in the comparator arm that did not contain Tenofovir, but there is much more of an effect in the Tenofovir-containing arms. This seems to be exacerbated in patients who are also receiving boosted protease inhibitors as part of their HIV regimens, and that's probably related to two transporters in the renal tubular cells. The changes don't

seem to be different in quality in the pediatric age group, although we have been concerned all along there might be quantitatively greater or have a bigger impact because of the aspect of growing bones.

And so we've proceeded very slowly and cautiously to evaluate the drug in pediatric populations. We have asked the company to build into the studies of younger children, some additional renal toxicity markers, and try to correlate those with the DEX of data to get a better handle on what's happening, and really hope those data will be forthcoming soon.

CHAIRMAN ROSENTHAL: Thank you, Dr. Lewis. Dr. Mink?

DR. MINK: Forgive me if you've mentioned this before and I missed it, but the question we're being asked to vote on refers to routine monitoring for children 12 years and older, or is this -- because there is a recent labeling change for children two years to 12 years. Is that being monitored in a separate manner, or can you clarify for me exactly what we're considering?

DR. MURPHY: So -- it's Dianne Murphy -- it'll come back to you within the labeling change. It'll trigger a safety review, so it will come back to you for that age group. I’m sorry.

DR. HEJAZI: No, it was the same thing I was going to say.

CHAIRMAN ROSENTHAL: Okay. Other questions? All right. So, the FDA is recommending routine monitoring in the age group specified, and the question is, does the committee concur. So, all who concur, please raise your hands. And opposed? Any abstentions? All right. Dr. Reed, will you get us started?

DR. REED: Michael Reed, I vote yes.

DR. RAKOWSKY: Alex Rakowsky, I vote yes.

DR. WAGENER: Jeff Wagener, yes.

DR. TOWBIN: Kenneth Towbin, yes, and I'll be very interested in what the bone marrow density studies look like in the 2- to 12-year-old group because, of course, one would be concerned about their...

DR. KRISCHER: Jeff Krischer, yes.

DR. JOAD: Jesse Joad, yes.

MS. CELENTO: Amy Celento, yes.

DR. RAIMER: Sharon Raimer, yes.

DR. LARUSSA: Phil LaRussa, yes, and a comment on the subsequent studies, the -- some kids who get Tenofovir as part of an optimized regimen, it would be very different than the kids who get Tenofovir as part of primary therapy, and those kids who probably get it as part of fixed dose combinations, so you may actually have to look at those separately.

DR. GLASIER: Charles Glasier, yes.

DR. MINK: Jon Mink, yes.

DR. WIEFLING: Bridgette Wiefling, yes.

DR. HEWITT: Geri Hewitt, yes.

DR. MOTIL: Kathleen Motil, yes.

DR. WHITE: Michael White, yes.

CHAIRMAN ROSENTHAL: Okay. Thank you, Dr. Hejazi.

DR. HEJAZI: Thank you.

CHAIRMAN ROSENTHAL: And, Dr. Santana, will you please join us again at the table? Thank you. All right.

DIFFERIN LOTION (ADAPALENE)

STANDARD REVIEW OF ADVERSE EVENTS

CHAIRMAN ROSENTHAL: Next we'll be talking about Differin lotion. There are no recusals that I'm aware of for this product. Dr. Erica Radden will be presenting the safety review for this product.

Dr. Radden is a family practice physician who received her medical degree from Uniform Services University of the Health Sciences and completed internship and residency training at Malcolm Grove Medical Center on Andrews Air Force Base with the National Capital Consortium. She recently separated from the United States Air Force after 14 years of service and joined the United States Public Health Service.

Prior to joining the FDA, she practiced at Bilbo [spelled phonetically] Air Force Base where she served as the medical director of the Family Practice Clinic in addition to deputy chief of the medical staff. So, we're very grateful, Dr. Radden, that you've come to present this to us today.

DR. RADDEN: Thank you. Okay. Today I'll be talking about Differin, or adapalene, lotion. I'll be following this familiar outline, adding additional context from prior safety reviews.

Differin 0.1 percent lotion is a topical retinoid

approved for the treatment of acne vulgaris in patients aged 12 and older that is marketed by Galderma Research and Development, Incorporated. Differin lotion was originally approved in March 2010, at which time labeling reflected the studies that had been completed to support its approval in adolescents, triggering this peer review. PREA was waived in patients under age 12 because necessary studies would be impossible or highly impracticable, due to the low prevalence of acne in this population. At the time of approval, additional pediatric studies were requested for pharmacokinetic data in adolescence under maximal use conditions for the due date of February 2012.

Epiduo, which is a combination of adapalene and benzoyl peroxide, was the focus of one of the previous pediatric advisory committees, and you will hear more about it in addition to the number of other Differin formulations.

The safety and efficacy of Differin was established in two double-blind parallel group studies lasting 12 weeks, which included patients ages 12 years and older with moderate, severe acne vulgaris. Patients were randomized to either Differin lotion or to vehicle. The studies included over 1,000 patients, over half of which were adolescents. Differin lotion demonstrated an improved investigator global assessment and lesion count versus the vehicle. These studies provide information on patients 12 years and over at the time of

approval that was included throughout labeling.

I’m now going to discuss relevant Differin safety labeling. There are no contraindications. The warnings and precautions section warns against ultraviolet light and environmental exposures, and discusses commonly seen local cutaneous reactions. These same cutaneous symptoms are noted adverse reactions. I’m sorry. As you can see there. Sorry. Let me go back one. The majority of these local skin reactions was transient, mild to moderate in severity, and managed with moisturizers. These local cutaneous symptoms generally peaked in severity in the first two weeks and then declined by week 12 of treatment. These are the percentages of the first two weeks, and then at week 12 of treatment.

So now that we've discussed the background and labeling information, let's examine the use of adapalene-containing products, and specifically Differin, to provide more context.

So adapalene-containing products were prescribed in about two million patients from March 2010 through December 2012 -- sorry, 2011 -- with over 40 percent of these patients being pediatric, as you can see here. Although the use of Differin lotion in particular constituted about 5 percent of those patients using adapalene-containing products, pediatric patients similarly comprised about 40 percent of Differin lotion use.

You can again appreciate the modest use in pediatric patients of Differin lotion, the product we're discussing today, compared with other adapalene-containing products. Additionally, its use has remained stable over time, as you can see here.

Dermatologists were the top prescribers of Differin lotion, with pediatricians accounting for 4 percent of dispensed prescriptions. The only diagnosis provided for pediatric patients was acne not elsewhere classified.

Now, let's turn our attention to safety. Prior safety reviews of adapalene-containing products have been conducted, including one in July of 2009 involving a report of phototoxicity in a 16-year-old that was taking adapalene and tetracycline. The timing of administration of the two products cannot be determined, however, and no action was recommended. There was another review in August 2010 in preparation for a PAC involving Epiduo post-marketing adverse event reports in children under 16 that identified hypersensitivity-related reactions.

Epiduo was presented at the December 2010 PAC, and the FDA was advised to revise the Epiduo labeling and the warnings and precautions and post-marketing experience sections to include the potential for hypersensitivity reactions in -- via a nearly unanimous vote.

The recommended labeling changes are underlined here.

Now, let's look at the adverse events. An adverse event review was conducted using the search terms Differin, adapalene, and all associated verbatim names from the date of the first Differin formulation approval of May 31, 1996. Of the 54 reports identified, 51 were noted to be serious.

We're going to walk you through how we developed our case series. Of the 51 serious pediatric reports, none were duplicates. After excluding 33 reports that were identified as non-serious and one report involving Epiduo that was captured in the previous Epiduo peer review, 17 reports remained with no reported deaths. As expected, the majority of cases involved adolescents. Three involved congenital anomalies, including one that was reported at age four. One case involved use at age 10. We will discuss these cases in more detail later.

So the 17 cases of serious, non-fatal pediatric adverse events have been grouped into the following categories: six dermatologic, with three of the cases involving currently labeled events and three of the cases involving unlabeled events. There were five central nervous system and three hepatabiliary events, all of which were unlabeled, and three events categorized as congenital anomalies. Of note, different is labeled as pregnancy Category C.

I will focus more on the unlabeled events and give an overview of the labeled events. The three labeled dermatologic

events involved a photoallergic reaction, application site sensitivity, and acute contact eczema. You will recall that the warnings and precautions section of the Differin label advises against sun exposure, and dermatitis, contact dermatitis, and eczema are reported in the adverse reaction section of Differin cream label.

Three of the dermatologic cases involved unlabeled adverse events. The first is a 10-year-old female who was diagnosed with erythema multiforme two months after initiation of adapalene cream. She was instructed to discontinue use but did not follow up. The second, a 16-year-old male, experienced thinning of the hair and receding of the hairline one year after adapalene use. He was also taking fexofenadine and esomeprazole, the latter of which is labeled for alopecia.

Finally, a 16-year-old female experienced angiodema 13 days after starting minocycline and 0.1 percent adapalene gel with a positive Mycoplasma titer. She improved after discontinuation of both medications. Of note, minocycline is labeled for angioneurotic edema and microplasma has been associated with urticaria and angioedema. Also, as you know, there is related labeling with Epiduo regarding hypersensitivity reactions.

There were five central nervous system events, all of which were unlabeled, that were further classified as

neuropsychiatric, neuromuscular, and general. The neuropsychiatric event was of a 16-year-old male that reported "lack of concentration, trouble focusing, trouble sleeping, anxiety, and was dispirited and depressed" 17 months after starting 0.3 percent adapalene gel. He was also using a topical clindamycin/benzoyl peroxide combination, which he continued, and recovered one month after stopping adapalene.

There was one report of a 16-year-old female who developed ptosis, muscular weakness, and difficulty swallowing three months after initiation of lymecycline, a tetracycline antibiotic, and topical erythromycin, adapalene gel, the latter of which was substituted for topical tratinoin. All these medications were stopped and replaced with a topical erythromycin/benzoyl peroxide combination, and she was ultimately diagnosed with myasthenia gravis.

I want to particularly draw your attention to the next three general CNS events. In the first, a 14-year-old female was hospitalized with intracranial hypertension after using 0.1 percent adapalene gel. No infection was detected on lumbar puncture, and she resolved without sequelae. It is unclear, however, if adapalene was discontinued. In the next case, a 13-year-old female also developed increased intercranial pressure one to two months after starting adapalene gel with resolution of symptoms after discontinuation.

Finally, a 14-year-old female also developed symptoms of intracranial hypertension five days after starting minocycline and adapalene gel. She was diagnosed with drug induced pseudotumor cerebri, with improvement after both medications were discontinued. The case may be confounded by the fact that minocycline is labeled for benign intracranial hypertension; however, idiopathic intracranial hypertension has also been associated with hypervitaminosis A and is labeled for the systemic but not the topical retinoids. You will also note that the reported weights for the adolescents in these three cases were within normal ranges for their ages.

There were three hepatobiliary cases that were unlabeled. In the first, a 16-year-old male developed elevated transaminase levels after taking adapalene for an unknown duration and isotretinoin for a day. He was noted to have globular hepatic lesions on liver biopsy. Adapalene was discontinued, but no follow-up information was provided. Although mild elevations of liver enzymes are noted in isotretinoin labeling, its use was brief in this single case of transaminitis.

A 15-year-old developed cholestatic jaundice and hepatitis two months after starting 0.1 percent adapalene gel and oral minocycline. He was subsequently diagnosed with hepatitis C and improved after discontinuation of both drugs.

Also, minocycline is labeled for both hepatic cholestasis and hepatitis.

Lastly, a 15-year-old male developed acute liver failure after using 0.1 percent adapalene gel for six months and taking oral erythromycin for an unknown period. The etiology remained unknown, and symptoms persisted despite discontinuation of adapalene. Of note, erythromycin is labeled for hepatic dysfunction.

Finally, there were three cases of congenital anomalies that were reported in mothers using adapalene during pregnancy. The first involved a neonate with one kidney, and the second was a case of neurofibromatosis reported in a 4-year-old. In the last case, the mother also used clindamycin and a topical antifungal liquid, and the neonate was born with multiple deformities with no detected chromosomal abnormalities. I remind you that adapalene is categorized as Pregnancy Class C.

This concludes the pediatric focus safety review. As a result of studies conducted under PREA, adapalene lotion is approved in patients 12 years and older. The safety review identified three cases of intracranial hypertension, all of which involved the gel formulation. The FDA is conducting a review of idiopathic intracranial hypertension and topical retinoids in all ages; however, no modification of adapalene labeling is recommended at this time. Does the committee

concur? And I'd like to acknowledge the contributors to this review listed on this slide. Thank you.

CHAIRMAN ROSENTHAL: Thank you, Dr. Radden. Questions for Dr. Radden? Dr. Radkowsky?

DR. RAKOWSKY: Thank you very much for your review. Is this review of [unintelligible] something in the near future that perhaps we'll hear the results of this, or is this something down the road? I mean, if we're going to vote to kind of maintain surveillance, does that include that there'll be an update in the near future about intercranial pressure changes and the retinoids?

DR. HAUSMAN: I can answer that. Ethan Hausman from pharmacovigilance. The review is underway right now, and we expect it to be complete in the near future. We can write review through Dr. Murphy, and it may get distributed to the AC according to whatever mechanisms that we have. But we think right now with what we have for the drug background from our standpoint, how we look at things, we don't necessarily think that there's going to be a need to come back to the committee. The review is not complete yet. There's some biological plausibility with these kinds of drugs while actually only two of the cases we have weight down, we actually also don't have height, so there's no way to normalize this for BMI to determine whether these kids were obese or not for their stature or

anything like that. But, again, as we said this morning for the other drug, going back through standard pharmacovigilance, we'll be updating that committee with the results of the review.

DR. MURPHY: There are a couple -- Dianne Murphy -- there are a couple ways we can handle it. We can -- we usually try to clarify this at the meeting. We can send an update to you electronically. We can basically bring it back if you want us to bring back an update to be presented to the committee. And I -- you know, we've never had this happen, but I guess if we send it to you electronically, and you had enough concern, we could take those concerns into consideration and then decide whether to bring it back. But, it's usually the first two that we've had, so probably never had a situation where we sent something to committee and then they told us they wanted to bring it back. But, those are three ways that we can do this.

DR. WHITE: Could you do it as a facilitated review?

DR. MURPHY: A facilitated review? What do you mean?

CHAIRMAN ROSENTHAL: Dr. White, can you speak into the microphone, please?

DR. WHITE: Could you just send it to one of the reviewers to go over it, and if that person is satisfied, then just don't bring it to the rest --

DR. MURPHY: Yes, actually, thank you for bringing up that new procedure. We could do that, too. I think maybe we

would have to find someone that had no conflicts of interest, and we could consider that, yes.

CHAIRMAN ROSENTHAL: Dr. Santana?

DR. SANTANA: Maybe our colleague on the committee, Dr. Raimer, can answer this for me. So, is it common practice for moderate to severe acne that patients get both topical retinoids and also systemic retinoids? And the lead-in my question is with the systemic retinoids, we have that agriculture [spelled phonetically] program where we can follow the pregnancy registration issues, but clearly with the topical ones, they are reported outside of that system. So, can you clarify first, is it a practice that people do both, or is this unique case --

DR. RAIMER: That's unique, and it's hard to tell whether the topical stopped when the oral started or not, but, no, because oral causes so much dryness anyway. You don't usually do both at the same time. Plus, you don't need them from the inside and the outside at the same time.

DR. SANTANA: Thank you.

CHAIRMAN ROSENTHAL: Yes, Dr. Joad?

DR. JOAD: I just have a process question. Is there a reason we have to make this -- make some sort of determination at this moment? It seems like the most important data is pending, and the concern is there. And is it, like, a legal

requirement that it be done today?

DR. MURPHY: Well, you can -- it's a requirement to make some recommendation. Now, you could recommend, as we said, that you want us to bring this back to you, so that could be a recommendation.

CHAIRMAN ROSENTHAL: Yes, Dr. Wagener?

DR. WAGENER: So, I was impressed that all of these events, including the increased intracranial pressure, occur in this age group, and I while think getting further information would be valuable, it seems that what I would like to propose is that in approving this for a routine monitoring, we request that a report come back to the committee simply stating the results of your evaluation, not that we look at the drug, but to let us -- update us in the future with what the results of that study was. As you point out, if a signal is seen there, this is going to be reevaluated anyway. But, I would like to hear the results of that study.

CHAIRMAN ROSENTHAL: Other comments or questions? Dr. Towbin?

DR. TOWBIN: Just one quick one. So, the PK studies were completed and submitted? Did I understand that right?

DR. RADDEN: I'll defer that to the --

DR. OUSSOVAA: Yes, it was submitted in February of this year, and it's under review.

DR. TOWBIN: And were the results that it behaves in this age group in the same way it does in older individuals, or there was no concern?

DR. OUSSOVAA: It is under review, so I cannot comment.

DR. TOWBIN: So, at some point, I guess I would want to make the comment that I hope that would come back to us as well.

CHAIRMAN ROSENTHAL: And can I just ask that our agency colleagues just identify yourself into the mics so that everybody gets the --

DR. OUSSOVAA: Tatiana Oussovaa, deputy division director for Safety, Division of Dermatology And Dental Products.

CHAIRMAN ROSENTHAL: Thank you so much. Yes, Dr. LaRussa?

DR. LARUSSA: So, you in the three cases of hyper -- of pseudotumor cerebri, do we know anything about the diet of those patients and their vitamin A intake?

DR. HAUSMAN: Ethan Hausman, no we don't.

CHAIRMAN ROSENTHAL: Other questions? So, I think I'm hearing that the committee would like to hear something about the results from the review process, and -- but we can still, I think, give you feedback regarding the plan for no labeling

changes at this time.

DR. MURPHY: Okay. So, maybe you could ask the committee, because obviously we have expressed a desire to see this data that when they vote, maybe they could say whether they have any other desire besides having to come back -- or we've had one electronic, one designated review. I mean, people can make comments, and we'll write them down as they go around as to how they'd like to see this come back to them.

CHAIRMAN ROSENTHAL: Okay. That sounds good. That's -- I think that's a great idea. So, but the other part of this question is does the committee concur with the recommendation regarding the ongoing safety monitoring in this review process? So, why don't we vote on that? And then, as we're stating our votes, we can go into a little bit more detail about how the committee would like to hear back on this review process. So, all in favor of continuing surveillance and continuing with this review process, please raise your hands. Very good. And any opposed to that approach? And have there been any abstentions? Dr. White?

DR. WHITE: I voted yes, and I would like to see it come back as an abbreviated review of the information that's being considered right now.

DR. MOTIL: Kathleen Motil, I vote yes, and I'm going to go with the abbreviated review.

DR. HEWITT: Geri Hewitt, yes, and yes also to an abbreviated review.

DR. WIEFLING: Bridgette Wiefling, yes, and yes to the review.

DR. MINK: Jon Mink, yes, and I also agree to an abbreviated review.

DR. GLASIER: Charles Glasier, yes, and also to the review.

DR. LARUSSA: Phil LaRussa, yes, and might as well do it on the, agreeable to an abbreviated review, yeah.

DR. RAIMER: Sharon Raimer, yes, and I should guess the committee, but it sounds like a good idea to do an abbreviated review to me.

MS. CELENTO: Amy Celento, yes, and I concur on the abbreviated review.

DR. JOAD: Jesse Joad, I'm also a yes, but it strikes me to come back to the committee for a review.

DR. KRISCHER: Jeff Krischer, yes, and I agree.

DR. TOWBIN: Kenneth Towbin, yes, and abbreviated review. Of course, if it doesn't meet the criteria for an abbreviated review, then it will be done differently.

DR. WAGENER: Jeff Wagener, yes, and I would actually like to see it come back to the committee, too, for a brief presentation.

DR. RAKOWKSY: Alex Rakowsky, yes, and just like what Dr. Towbin said, if it matches abbreviated review criteria, then I think that's fine. If not, then it goes back to committee.

DR. SANTANA: Victor Santana, and I won't repeat it, but I also agree with what was just said a minute ago that if it's abbreviated, we can handle it that way, but if it's more detailed, it needs to come back to the committee.

DR. REED: Michael Reed, I voted yes, and I agree.

CHAIRMAN ROSENTHAL: All right. Thank you. And I'll just make a comment that we're all guests, and that we've been invited because of our unique expertise and insight into these. So, you should all feel comfortable sharing any ideas that we have about how best to review these issues.

MULTIHANCE INJECTION (GADOBENATE DIMEGLUMINE)

STANDARD REVIEW OF ADVERSE EVENTS

CHAIRMAN ROSENTHAL: So, now we'll move on to MultiHance, and, again, Dr. Radden will be presenting this product. So, Dr. Radden.

DR. RADDEN: Okay. For the next review, I'm going to discuss MultiHance or gadobenate dimeglumine. We will again be following this familiar outline.

MultiHance is a gadolinium based contrast agent that is approved for intravenous use in magnetic resonance imaging of the central nervous system in adults and children over age two to visualize lesions with abnormal blood brain barrier or abnormal vascularity of the brain, spine, and associated tissues. It is administered via rapid bolus IV injections at 0.2mL per kilogram and marketed by Bracco Diagnostics, Incorporated.

MultiHance was originally approved in November 2004, at which time PREA studies were waived in patients under two years of age due to safety concerns related to nephrogenic systemic fibrosis, or NSF, which will be discussed later.

Studies were required for safety and efficacy in patients two to 16 years and for pharmacokinetics in patients aged two to five years with known suspected CNS disease. That

requirement was fulfilled in March 2010 with the Langlin [spelled phonetically] change prompting this review.

Safety and efficacy of MultiHance was demonstrated in a multicenter open labeled study that compared contrast enhanced and unenhanced brain and spine MRI's in 92 children and adolescents with known or suspected CNS disease. Superior lesion visualization was seen on enhanced images relative to non-contrast images which was comparable to the results in adults. The results from this study extended the indication from adults to children down to age two. The studies conducted in pediatric patients were summarized in the pediatric use section, and the possibility of increased risk of NSF in patients less than age two is noted. Information is included throughout the labeling on safety and will be discussed in context.

Now we will discuss the relevant MultiHance safety labeling, focusing on conditions which you will see again in the review. Let's begin with the boxed warning for NSF. An increased risk of NSF is associated with the entire class of gadolinium-based contrast agents, particularly in patients with impaired renal elimination, such as those with chronic severe kidney disease or acute kidney injury. Screening for renal impairments is recommended prior to use of these agents. MultiHance is contraindicated in patients with known allergic or

hypersensitivity reactions to these contrast agents. You will see this also discussed in the warnings and precautions section.

As you can see, there are six subsections to the warnings and precautions section, but I want you to pay particular attention to the first three -- NSF, hypersensitivity reactions, and acute renal failure, which will appear again later.

Clinical trial experience in pediatrics did result in labeling changes in the adverse event section reflected here. The most common pediatric adverse event, same with MultiHance, include vomiting, pyrexia, and hyperhidrosis, which is comparable to adult adverse events. You will see that hypersensitivity reactions were noted in post-marketing experience. These concerns were communicated in patient counseling information as well.

Now let's look at the use of MultiHance. So, as you can see, the use of MultiHance continues to rise. These figures show that use is highest among adults, with about 4 to 6 percent use in approved pediatric ages of two to 16, and approximately 1 percent use in unapproved patients under age two.

Now we'll turn our attention to safety. You will notice that less than 1 percent of adverse events were reported in pediatric patients. Of the 36 pediatric adverse events reported since the approval of MultiHance, 12 were deemed

serious, which included five deaths. Two pediatric reports were also noted among the null values, one of which was fatal, giving a total of 14 reported pediatric adverse events.

I will now walk you through the case selection. Recall that we began with 14 total pediatric reports, including six deaths. Four of the fatal reports were duplicates. There were 10 remaining unduplicated reports, two of which were deaths. One report of a 54-year-old patient was excluded as it was miscoded, leaving us with nine serious pediatric cases, two of which involved fatalities.

I will first discuss the fatal reports. In the first, an 11-year-old male experienced anaphylaxis with unsuccessful attempts at resuscitation. He had undergone an uneventful MRI with a different gadolinium-based contrast agent three months earlier. You will recall MultiHance labeling of hypersensitivity reactions. In a second case, a 15-year-old male with renal failure did a large cell lymphoma of the kidney suffered a cardiac arrest. He had been diagnosed with NSF six months prior to his death and had received multiple gadolinium-based contrast enhanced MRI's in the year prior to his death, of which MultiHance was not confirmed. He also had a history of chemotherapy-related cardiomyopathy and an unspecified pulmonary complication with bleomycin. You will recall MultiHance labeled for NSF as well. Also, bleomycin is labeled for pulmonary

fibrosis. Both of these reports are related to labeled events.

Of the remaining serious pediatric cases, seven were non-fatal and have been grouped in the following categories: five hypersensitivity, one accidental overdose with necrotizing colitis, and one report of NSF. You will notice that unlabeled adverse events are underlying, and there was only one.

I have provided details about the hypersensitivity events, but as they are labeled, I will not focus on them. Four events involving hypersensitivity reactions in adolescents were reported. One case involved a 30-month-old who was presedated with propofol. Again, hypersensitivity reactions are noted in MultiHance labeling, and risk of anaphylactic reactions is also noted in propofol labeling.

There is one case involving the diagnosis of NSF in a 16-year-old male with a history of chronic renal failure secondary to reflex nephropathy. He had received two different gadolinium-based contrast agents in the year prior to his diagnosis, and MultiHance use could not be confirmed. Again, recall safety labeling for NSF.

This last report involves the single, unlabeled, non-fatal adverse event. A full-term neonate accidentally received a tenfold excess dose of MultiHance during evaluation of a lipomyelomeningocele. She subsequently developed necrotizing enterocolitis, or NEC. This single event is confounded by the

association of NEC with her underlying condition and a tenfold overdose of MultiHance.

This concludes the pediatric focus safety review. As a result of studies conducted under PREA, labeling has been changed to reflect MultiHance's indication in pediatric patients two years and older, and no new pediatric signals were identified, and the FDA recommends a return to routine monitoring. Does the committee concur? And I'd like to acknowledge the folks on this slide. Thank you.

CHAIRMAN ROSENTHAL: Thank you, Dr. Radden. Questions for Dr. Radden regarding this agent? Yes, Dr. Hudak.

DR. HUDAK: Just curious what the osmolality of the solution is on injection.

DR. RADDEN: I'm sorry, I didn't hear the question.

DR. HUDAK: The osmolality of drug? Do you know?

DR. RADDEN: I will defer that to --

DR. HUDAK: The reason I ask is because in the past with cardiac catheterization procedures, highly osmolar agents used in large qualities correlated with NEC in term babies.

DR. KREFTING: Hello. This is Ira Krefting from the division of medical imaging products.

CHAIRMAN ROSENTHAL: Sir, your mic is off.

DR. KREFTING: Can you hear me now? I can't give you an exact answer to that, but this has been one of the issues

that we've held in discussion and peripherally. I'm not aware exactly of the osmolality of the agent. I think it is the new, in the medium range for the gadolinium ranges in general.

CHAIRMAN ROSENTHAL: Other questions from the division for this speaker? All right. Well -- thank you, Dr. Wiefling.

DR. WIEFLING: I just have a quick comment on patient labeling. So, I see this a lot, and I just want to bring it to the attention as more labels are being developed and the way in which we sort of communicate how the physicians are going to be asking the questions or the patients are going to be receiving them. It seems really minor and maybe stupid, but under Section 17.1 where it says nephrogenic systemic fibrosis, and you're supposed to counsel the patient before you obviously inject the medication, it says, you know, basically instruct the patients to inform you if they have any kidney disease or liver disease, and a lot of times patients take that when you ask them that question because they go to a specialist, and the specialist just say, "Oh, everything looks great, we'll see you in six months." They don't really necessarily always understand that they have a disease that's being monitored and is under control. And, so, you know, you may want to be actually asking them, "Do you have any kidney or liver disease that you know of, or are you seeing a specialist for the kidneys or your liver?"

And then the other one is the second question, which

I've run into personally, is when you ask if they've had the dye before. They don't know the difference between CT dye and they don't know the MRI dye, and so you have to really ask, you know, have you received any kind of dye, basically, in general, CT or MRI, and sort of ferret that out. Thanks.

DR. MURPHY: It's 1.970 osmoles per kilo at 37 degrees. That viscosity and density.

DR. KREFTING: I was going to give you that data in another form at six point times that of plasma. Okay. So, that's -- it's a hyperosmolar solution. Yeah. In answer to the other panelists -- state their questions, I fully agree with many of the points you've made. This has been concerns as we dealt with the labeling of this and all the gadoliniums. The additional important teaching point that we've tried to make around the country is that this specific gadolinium agent administered to a given patient needs to be recorded. This, sadly, was not being done earlier in this past decade and certainly in the last century. So, I concur, and it is something being emphasized in our discussions.

CHAIRMAN ROSENTHAL: Yes, Dr. Glasier?

DR. GLASIER: Yes. Just one comment about the high osmolarity. It's true, it's a potential toxicity, especially if the gadolinium agent you're getting a much lower volume of contrast than you would with intravenous contrast or CT or

cardiac CAT or so forth.

CHAIRMAN ROSENTHAL: Dr. Joad.

DR. JOAD: Is NSF a concern for all gadolinium agents?

DR. RADDEN: Yes, yes.

DR. KREFTING: Yes, well, allow me to elaborate. Again, to review for everybody here at the committee, NSF is nephrogenic systemic fibrosis. It's a recently described entity in that it involves skin changes, which in many cases are fairly characteristic, and ongoing fibrosis of multiple internal organs such as the lungs. In a -- perhaps 10 percent to 30 percent of cases, it has proved fatal, and there is no specific treatment for it after a long detailed -- after the neurologic studies that -- and an association with gadolinium agents has been observed and fairly well documented, particularly in previous advisory committees and multiple publications around the globe.

So, we believe that all gadoliniums to some extent are associated with NSF. We feel that this is a, obviously, a class of agents, but the risk for NSF is not uniform among the class. And, in fact, we have subdivided the class into agents, which are more associated, if you wish, with NSF -- that being omniscan [spelled phonetically], activist [spelled phonetically], and optimart [spelled phonetically]. MultiHance falls in a category where there is less of an association. Exploration for this reason is still ongoing. It may be related

to less use of mezropolene [spelled phonetically], use of a lower dose, or it may just be a formulation that is less associated for the various physical chemical reasons.

So, the answer to the question is our concern remains for all the gadolinium agents.

CHAIRMAN ROSENTHAL: Dr. White.

DR. WHITE: Much of the review of the information going through it emphasizes the concern about using under one year of age because of renal function in those patients. Is there any action we can take to further emphasize the potential risks for these children in using these agents under one year of age? It's used in cardiology, I know, or cardiac MRI, or gadolinium agents are, and we're getting more and more involved in its use, so can we do anything to help that?

DR. KREFTING: We are aware of its use in this unlabeled age group. Clearly it is of concern for the physiologic regions mentioned in the presentations, mainly on the development of the kidneys and diminished, conceivably diminished excretion in those younger age groups where the gadolinium will stick around longer within the system and stimulate a cascade of immunologic events conceivably leading to NSF. Notice all of my words are conceivably maybe because this is still an area of great study.

To get back to your question of the -- we realize it's

used in cardiology, for which off label in this age group where there are very sadly, hopelessly, severely ill children with multiple cardiac effects, and we've been told by our pediatric cardiology folks that it's really very necessary to define possible surgical interventions in that age group.

So, we've backed off from using regulatory discretion in dealing with and realizing this is a severely ill group of children. To wait, however, the academic community is quite aware of the things you've mentioned, Dr. White. I believe there is a publication that is now public, looking at the dosing of pediatric cardiology patients in this age group, considerable discussion within the academic community. I can't give you a specific response now, but it is an area of intense discussion.

CHAIRMAN ROSENTHAL: Thank you for the question and that very thorough response. Are there any other questions?

All right. Well, we're being asked whether we concur that the -- with the FDA's recommendation to return this product to routine monitoring, and as we learned earlier, routine monitoring is a robust process. All in favor of returning it to routine monitoring, please raise your hands? Okay, any opposed? And any abstentions? All right. Dr. Reed, will you get us started?

DR. REED: Sure. Michael Reed, I voted yes.

DR. SANTANA: Victor Santana, I vote yes.

DR. RAKOWKSY: Alex Rakowsky, yes.

DR. WAGENER: Jeff Wagener, yes.

DR. TOWBIN: Kenneth Towbin, I concur.

DR. KRISCHER: Jeff Krischer, yes.

DR. JOAD: Jesse Joad, yes.

MS. CELENTO: Amy Celento, yes.

DR. RAIMER: Sharon Raimer, yes.

DR. LARUSSA: Phil LaRussa, yes.

DR. GLASIER: Charles Glasier, yes.

DR. MINK: Jon Mink, yes.

DR. WIEFLING: Bridgette Wiefling, yes.

DR. HEWITT: Geri Hewitt, yes.

DR. MOTIL: Kathleen Motil, yes.

DR. WHITE: Michael White, yes, with the request that the FDA look at ways to require safety data in children under one year of age.

CHAIRMAN ROSENTHAL: So we're 20 minutes ahead of schedule. My inclination would be to do one more product before going to the break if that sounds okay, and maybe we can shift the afternoon up a little bit? I understand that there's an important conference call that's going to happen exactly at the end of the meeting.

DR. MURPHY: They have the division here for Dulera.

CHAIRMAN ROSENTHAL: Yes, I see. Either a hand went

up, or they're doing the wave in the back row. OSU's prepared.

Okay. Let's move ahead, then.

DULERA INHALATION AEROSOL (MOMETASONE FUROATE AND FORMOTOROL FUMARATE) STANDARD REVIEW OF ADVERSE EVENTS

CHAIRMAN ROSENTHAL: So, I'll talk more slowly than usual to give people time to move into their seats, and I'll just remind - first, thank you to the representatives from the last division. I appreciate your input. And then as people from this new division come up to the table, I just remind you that at least the first time that you speak into the mic, please introduce yourself so we know who's addressing the committee.

There are two recusals from this, from the discussion of this particular product, Drs. Hewitt and Raimer, and we'll call you back after we've had a chance to discuss Dulera.

So, the next product is Dulera inhalational aerosol and will be presented by Dr. Elizabeth Durmowicz, who joined pediatric and maternal health staff in 2008. She received her medical degree from University of Cincinnati College in Medicine and completed her internship and residency pediatrics at the University of Colorado Health Sciences Center.

Dr. Durmowicz's area of clinical interest is the care of children with special health care needs, and she has practiced in both academic and community care settings. And, you know, to say as well that Dr. Durmowicz has helped us in

many of these with reviews, and as with the other medical officers, we really appreciate the information you've provided. So, Dr. Durmowicz.

DR. DURMOWICZ: Thanks, Geoff. So, I'll be presenting the pediatric focus safety review for Dulera. My presentation will follow the following outlines, so much of the other safety reviews, but I would like to point out that in addition to a review of pediatric adverse events associated with Dulera, I will also present a review of adverse events associated with the single ingredient formoterol product Foradil.

Dulera is a combination inhalational aerosol product containing mometasone, cortical steroid, and formoterol, along acting beta-II agonists. Two formulations of the product are marketed. The formulations provide different doses of mometasone, but the same dose of formoterol. The product was originally approved in June 2010 and is approved for the treatment of asthma in patients 12 years of age and older.

I'd like to point out that both the single ingredients are also approved as inhalational agents in asthma, mometasone, specifically Asthmanex, is approved in patients four years and older and formoterol, specifically Foradil, is approved in patients five years and older. The approved dosing is provided in this table that is from labeling and is based on previous therapy. At the time of approval in June 2010, the pediatric

requirements of study under PREA were waived in patients zero to four years and a third in patients five to 11 years.

Dulera has a risk evaluation and mitigation strategy to inform health care providers of the risks and appropriate use of long acting beta agonists and the elements of the REMS [spelled phonetically] include a communication plan a well as a timetable for submission of assessments.

The safety and efficacy of Dulera were demonstrated in two pivotal clinical trials. These were both randomized, double-blind, multicenter trials in patients 12 years of age and older with persistent asthma. The first trial was a 26 week trial and 781 patients, which compared Dulera to placebo and to its individual components. The second trial was a 12 week trial with 728 patients, which compared two doses of Dulera to mometasone. The efficacy results in the adolescent patients were similar to those in adults.

The safety database included three clinical trials, the two pivotal efficacy studies and a long-term active comparator trial. A total of 950 patients were exposed to Dulera. The pooled data from the 12 to 26 week trials identified that nasopharyngitis, sinusitis, and headache occurred in an incidence of 3 percent or more in Dulera treated patients and greater than placebo. Safety outcomes from the 52 week trial were similar in those to the 12 to 26 week trials

with the exception of dysphonia, which was observed at a higher frequency in the long-term trial. No differences in the type or frequency of adverse reactions were identified in the adolescent patients compared to those in adults.

I'll now move on to the pertinent information and labeling. Dulera includes a boxed warning for asthma-related deaths, which is information included in all Laba [spelled phonetically] product labeling. The boxed warning notes that available data from controlled clinical trials suggests that Labas increase the risk of asthma-related hospitalization in pediatric and adolescent patients.

Dulera's contraindications include primary treatment of status asthmaticus or other acute episodes of asthma, and labeling includes 16 warnings and precautions, all are consistent with known adverse events associated with Laba or cortical steroid use. These warnings and precautions are provided here and on the following slide.

I'd like to point out subsection 5.11, the warning on cardiovascular and CNS effects. It warns of excessive beta agenetic stimulation, resulting in nervousness, headache, tremor, dizziness, and insomnia, and these are some of the adverse events that we will see in our review. The warning in subsection 5.13 states that orally inhaled corticosteroids may cause a reduction in growth velocity when administered to

pediatric patients.

The adverse reaction section summarizes the safety from the clinical trial experience and the post-marketing experience subsection includes anaphylactic reaction. Section 7 provides information about metabolic pathways and/or classes of drugs for which the Laba in cortical steroid components may cause drug interactions and does note that additional advaneric [spelled phonetically] drugs may potentiate sympathetic effects.

The pediatric use section describes the safety and efficacy data from patients 12 to 17 years, states that safety and efficacy are not established in patients less than 12 years, and provides information about the potential for reduced growth philosophy and provides monitoring and management recommendations.

The clinical pharmacology section under the pharmacodynamic subsection includes a summary of APHPA access trial results and the patient counseling information includes safety warnings, and the medication guide is also included in approved product labeling.

This slide provides sales distribution data from the manufacturers to various retail and non-retail channels of distribution over an approximately three and a half year period. I don't think that's coming up there.

So, starting with June 2008 through December 2011.

The number of doses sold of Dulera are in dark blue at this right hand side of the graph. The doses of Perforomist, the formoterol inhalational solution, are provided in pink, and the Foradil Aerolizer, a formoterol product delivered by powder inhalation, is provided in green. And this dip actually represents a problem with a drug shortage. As you can see, there was a decrease in overall Foradil doses, and an increase for Perforomist doses sold. Approximately 35 million doses of Dulera were sold from manufacturers from July 2010 through December 2011. Whoops. Sorry about that.

This table provides the number of prescriptions dispensed and the number of patients receiving prescriptions for Dulera based on age. The section of the table on the right shaded in blue represents the age groups in which Dulera use is not approved. Of note, the numbers in this table are different from the numbers in your pointed review, and the data will be analyzed in March so that we are able to break down the zero to 11 year age group into the zero to four year age group and five to 11 year age group.

During the cumulative period of 18 months, approximately -- you can see that approximately 375,000 prescriptions of Dulera were dispensed to little over 100,000 patients. As you can see, a little less than 6 percent of prescriptions dispensed and total patients receiving dispensed

prescriptions for Dulera were aged 12 to 16 years, roughly 5 percent of prescriptions dispensed in total patients were aged five to 11 years, and less than 1 percent of prescriptions dispensed in patients receiving prescriptions were in the zero to four year age range category. Asthma was the top diagnosis for all age groups.

This pie charts shows a number of dispensed prescriptions by Dulera by the top 10 prescribing specialties from U.S. outpatient retail pharmacy. The areas shaded in the cornflower blue, it looks like, or purple up in your screen, represents general practice, family medicine, doctor of osteopathy specialists, and that's the top prescribing specialty, followed by allergy immunology, internal medicine, and pulmonary disease specialists.

I'll now move on to the safety reviews for Dulera and Foradil. The AERS database was searched for adverse events associated with Dulera combination products and all associated trade names and verbatim names during the approximate 18 month period since the time of approval in June 2010 through December 2011. As you can see, there are a total of 137 reports; 13 of these reports were pediatric reports, 12 were serious reports, and there were no deaths. The four age unknown reports with an outcome of death were reviewed, and there were no pediatric patients in that group.

This slide summarizes how the cases were selected of the 12 total serious adverse event reports. There were two duplicate reports. That left us with a case series of 10 unduplicated reports. None were excluded, so we did have a remaining 10 identified cases to review.

This slide provides some characteristics of the cases. As you can see, six of the 10 patients, six of the 10 reports were in patients in an unapproved age group -- so this was here -- and four of these six reports were in pages two to five years. The dosing ranged from one inhalation of a lower dose product to two doses of the higher dose product, which is the maximum recommended dose. The indications, the majority were in asthma; however, three cases did not report the indication for use.

Looking at the cases more carefully, as mentioned, there were no fatal serious adverse events. Of the 10 serious adverse events, seven were neuropsychiatric events, two were respiratory events, and one was considered in the other category. Although the focus of the review was on pediatric events and serious, unlabeled events, no reports of other adverse events of interest were identified.

I'll now move on to the identified cases, and I want to point out that the unlabeled adverse events will be underlined on all the slides.

There are five -- of the seven neuropsychiatric events, there were five reports of aggressive behavior. Four of these cases represent use in patients in the unapproved age group, and two of these cases reported administering the maximum recommended dose. The first case was that of a two and a half year old boy with aggression, changes in behavior, and changes in sleeping pattern one week after starting Dulera. The Dulera was discontinued, and the patient recovered. This patient was on albuterol as needed.

The second case was also a two year old boy with aggression, biting, weeping, and overall behavior change, but which occurred one week after starting Dulera. The Dulera was discontinued, and this patient also recovered. This patient also was on albuterol as needed.

The third case was of a four year old girl with mood changes, specifically aggression, sleep disorder, nervousness, jitteriness, and agitation after one year of Dulera use. In the past, this patient had had similar symptoms with budesonide formoterol inhaler, and this -- these symptoms had resolved with a lower dose. This, at the time of the report, the patient was having symptoms, and didn't -- Dulera was still being used.

The fourth case was a 4-year-old girl with aggressive behaviors after one week of Dulera. The product was discontinued, but we don't have a report on the outcome of this

case.

The fifth case was a 15-year-old boy with headache, aggressive behavior, and cough for four days after initiating Dulera. The Dulera was discontinued, and the symptoms resolved. This patient had what was reported as an allergy to fluticasel [spelled phonetically] and celmeturol [spelled phonetically]. This slide describes the two additional neuro-psych reports. One was a 15-year-old female with a tremor and was jittery for one day while she was on Dulera. The product was discontinued and the symptoms resolved. The start of Dulera did not result in similar symptoms.

There was also a 15-year-old girl who developed ticks within a few minutes of her first dose of Dulera. She was seen by a child neurologist at the Chop [spelled phonetically] ER and was diagnosed with acute motor and phonic tics. She was sent home without a treatment and follow-up. This patient had taken two caffeine-containing OTC products the day before and to the best of what I could see, it looked like she probably had about 380 milligrams of caffeine the day before.

There were two respiratory events reported. The first was a report of cyanosis and the specific wording from the report was feeling tired, vomiting, clammy, eyes glossy, lips turn blue and skin color was gray 10 minutes after the second omalizumab injection. This patient was treated with

epinephrine, montelukast, hydroxyzine, albuterol, and dexamethasone. Omalizumab was considered the primary drug of concern and therapy was discontinued with that product.

And as I note on this slide, Dulera is labeled for anaphylactic reaction, but Omalizumab also has a boxed warning for anaphylaxis and hypersensitivity events.

The second respiratory event was a case of bronchial spasm in a 10-year-old boy. Our other case was a 14-year-old girl with shortness of breath, shallow breathing, dizziness, sore throat and chest pain. Two of these episodes resulted in treatment and evaluation in the emergency department but we don't know the outcome.

Moving on to Foradil, formoterol was approved as a single ingredient and in combination for the treatment of asthma and some pediatric populations and in adults with chronic obstructive pulmonary disease. Foradil or formoterol fumarate is a powder inhalation treatment and approved for asthma in kids five years of age and older.

Symbicort, which is a combination of budesonide and formoterol is also an inhalation aerosol for treatment of asthma 12 years of age and older.

So AERS search for all reports of adverse events associated with the product term Foradil, for the the 30-month period from June 2009 to December 2011, and seven pediatric

events were identified. Five of these reports were excluded secondary to concomitant medications and the two remaining cases I summarized briefly on this slide.

The first was a 13-year-old girl who was hospitalized with an enlarged and painful stomach. The patient recovered and it was a little bit unclear about the challenge, rechallenge, but she did get better at some point with Foradil temporarily interrupted. And the second case was actually a case of transplacental exposure.

So in summary, the pediatric safety review identified five reports of aggressive behavior and unlabeled event. Four of the reports were in patients four years of age and younger -- an unimproved age group. Although the FDA does not recommend labeling changes at this time, the agency intends to continue routine postmarketing monitoring, including monitoring of pediatric neuropsychiatric events as well as continue monitoring of the ongoing Dulera clinical trials in pediatric patients five to 11 years. And we're interested if you concur and your comments. I'd like to thank the following individuals for their help with the presentation.

CHAIRMAN ROSENTHAL: Thank you, Dr. Durmowicz. Questions or comments from the committee? Yes, Dr. Mink.

DR. MINK: Well I want to apologize in advance for bringing up this issue again, but I'm struck by how many of the

serious adverse events are related to off-lable use and it's not the FDA's role to tell physicians don't do this but I am curious about what ongoing Dulera clinical trials in the younger age children, and I'm not entirely comfortable with the idea that just routine monitoring, giving what we just heard, that I think they're -- something we need to hear little bit more about in the younger age.

CHAIRMAN ROSENTHAL: Can you please identify yourself too, before speaking into the mike if someone from the agency's going to jump on that.

DR. CHAUDHRY: My name is Dr. Sophia Chaudhry from the allergy and rheumatology products. So there are six PREA commitments for Dulera, for the five to 11 age range group. Sorry. There are six PREA commitments that are ongoing in the age five to 11 age group. Two are regarding with and without spacer [spelled phonetically] use for the PK and pharmacodynamic trial. There is an APA access trial as well as a safety and efficacy trial, and a long-term safety trial. They're all ongoing, or planned

DR. MINK: Same dosing as in the older group?

DR. TONY DURMOWICZ: This is Tony Durmowicz. I’m from the lesser half of the Durmowicz family here today. There's a dose ranging, study especially with formotorerol and [unintelligible] before that, for the safety and efficacy trials

where multiple doses are being assessed.

CHAIRMAN ROSENTHAL: Dr. Joad.

DR. JOAD: Yeah, as an unusual event that happened -- these aggressive behaviors are very familiar to anyone who's given oral Prednisone to a child. So it seems like there's biological reason in this, but this could be related to the aggressive behavior. And then it's probably quite rare and that makes me worried that their study wouldn't pick that up. There's certainly certain children who have severe growth suppression from inhaled steroids although it's very rare. So to me it seems like it would be a good idea to make it be a warning unless there's some reason you can't -- you shouldn't do it because it did occur in the younger age for which it's been approved.

CHAIRMAN ROSENTHAL: Yes, Dr. Hausman.

DR. HAUSMAN: Yes, to provide a little more expansion on the aggressive behavior events, I was just pulling up the adverse effects reports of the -- and this is not to minimize the way the reports were presented to the committee. In one of 2-and-a-half-year-old children, they were actually receiving two steroid containing compounds at the same time, both containing the medicine [spelled phonetically] -- one Dulera, one Nasonex. One of the 4-year-olds -- or actually the other 2-and-a-half-year-old was receiving concomitant albuterol and there's -- it's

unclear at what later date the aggressive event resolved. Moving on to the first 4 year old, they were on Dulera, Colmecort [spelled phonetically], Foradil at the same time. Evidently, the second four-year-old was -- just as it was described, and there's also no additional information in the 15-year-old. So that's just give the -- a little bit more background on these particular cases.

CHAIRMAN ROSENTHAL: Dr. Wagener.

DR. WAGENER: Dr. Durmowicz, could you clarify -- one of your slides you commented that the PREA was waived in the zero to 4 and deferred in the five to 11. What does it mean to waive it or to defer it?

DR. DURMOWICZ: So when a new product is approved, there are specific triggers that would invoke the law of the Pediatric Research Equity Act, and if there's a new indication and essentially a new drug, then we can require studies in certain -- in the pediatric population. And the agency makes the determination in which age groups those studies would be appropriate. And so in this case situation, the division may be able to talk to this more carefully. It said it was chosen that studies in patients less than five years would not be appropriate for this product. The patients -- but additional information, it was needed in patients five to 11 years.

DR. MURPHY: So what that means -- if I could clarify

a little more. It means the agency has said you don't think you should study it; we're going to waive it. So we've basically given up our authority -- not 100 percent -- to go back and say no we've changed our minds, it's very difficult that we want to study in that age group. So just -- we weighted something, that's a pretty strong signal that you're not going to ask for studies. We think there's reason not to do it. Deferral means that we think you need to study it and we need to talk with you about what kind of studies and get those studies done.

CHAIRMAN ROSENTHAL: Yes, Dr. Wagener.

DR. WAGENER: So following on that, does it concern you that the way events occurred in the under 5-year-old or supposedly there are less than 2,000 prescriptions out there. In other words, physicians are using it in that age group and it appears that there's a very high number of adverse events relative to the number of prescriptions.

DR. MURPHY: That's not for me to answer. That's for you guys to discuss. That's why we're here.

CHAIRMAN ROSENTHAL: Okay. Dr. Wagener, would you like to discuss it? Do you want to go -- you reflected on asking a question but would you like to reflect on it further or --

DR. WAGENER: I wouldn't ask an indirect question like that without a feeling of -- I would agree with Dr. Joad that,

you know, there is one there is plausibility with the steroid component that you get the neurologic effects. There was nothing presented today about the growth effects because, obviously, that's not a big signal as far as adverse effect. But that would be another thing in that these newer steroids that are highly bound. The possibility of these problems increasing, so I would think that maybe the waiving is not the way to go and that there should be further evaluation, particularly the youngest age group, as far as toxicities.

CHAIRMAN ROSENTHAL: Now the waiving is -- that's a historical comment, right, it's already happened?

DR. WAGENER: The waiving is the waiving of -- prewaived for the zero to the 4-year-old.

DR. SACHS: This is Hari. The waivers already occurred and most likely, I mean -- and Tony you're-- you know from the division [unintelligible] probably the reason was because there's, you know, the formulation was not a good one to deliver to the kids and there weren't -- you know, they didn't think the studies were feasible. I don't think it was for safety.

DR. TONY DURMOWICZ: I'll try to address a little bit. I mean, when you go back -- this is a combination product and when we think about waiving something, we look at several factors. One is the safety of the products in combination and

we all have discussed safety of LABAs probably in this advisory committee and many, many other advisory committees over the past six to eight years, which is going to partially result in every manufacturer of a LABA doing a large clinical safety study, including in children.

But the safety of the LABA is in box warning. The inhaled corticosteroids have their own sort of side effects, which are in the class effects adverse events section in warnings and precautions. The reason to waive less than four years of age with a leader-dose inhaler isn't a delivery issue. It's more of a this is a fixed dose combination and should a fixed dose combination be used in a spectrum of young patients who are going to be, you know, quite different in weight, quite different in activities. You have two to four, two to six when they're like that.

So if you have one that's safer to use them individually, if you're going to use them at all, and we discourage the use of any single LABA by itself ever, and that's in the box warning. So they're the main reasons why we don't want it to be studied and we don't want it used in anybody less than four and five years of age, and it's -- without taking it off the market, which has been discussed, there's not too much more stringent things we can do without the REMS and without box warning in the labeling, in a labeling situation. So it's, like

I said, it's mostly safety but it's also the appropriate use of combination product in somebody that young that we waive those products.

Secondly, we know from the ingredients in the combination product formetasone [spelled phonetically], been around for a very long time, and has formoterol. So we view it as a combination of convenience, and as again like I mentioned you can use the individual components by themselves if you want to. But that's the main reason.

CHAIRMAN ROSENTHAL: Thank you, Dr. Durmowicz. Dr. Sachs, your mic is on. Do you have something else to add? Okay. Dr. -- oh, I'm sorry -- Ms. Celento?

MS. CELENTO: So Dr. Raimer asked does this concern you and I realize that's not for you to answer, but it concerns me as a parent and what we just heard -- I'm sorry, but there's sort of a circular logic that's happening. You know, we don't really want the drug prescribed, so we're not going to encourage studying it, we're going to waive studying it. And I'd like to just refer to Jeff's comment earlier about the work on the Pediatric Ethics Subcommittee. And, you know, it's just not even ethical to say we waive it because we don't want it studied yet, we know there are 2,000 prescriptions -- really, as a parent I'd sit here and say, you know, at this point the FDA is not protecting my child. So, I'm not trying to accuse anyone but

I'm a little bit baffled, and again, I think it's this circular logic that's not going to work if you're a consumer.

DR. TONY DURMOWICZ: Just to apply, I think the whole thing is circular, as is your logic. I mean, when we approve a drug, we do not have regulatory authority over an individual private practitioner. So I think it's immoral -- not a immoral, that's a bit over -- but unethical for a private practitioner to look at that label and know the doses with a boxed warning and give it to somebody who's two years of age, personally. And I think there is some onus on that private practitioner when they take the practice of medicine into their own hands to an individual patient, especially a young patient. So I think that you can argue from both sides.

DR. DURMOWICZ: I just want to say, I mean, the committee here is trying but there is something that should be in the label that is not there that would somehow enhance people understanding the concern. That's what we want to hear from you, you know. We think we've labeled it as best as we could but if you don't think it's -- and that's why these products come to you -- is that, here's what we've done, here's what's happening now, it's out there, you know, and if you think that the way it stands right now, knowing that, again, the studies of the committee are in the older five to -- we're not going to get any -- we're not going to get any other studies -- if you have

recommendations, then that's what we're here to discuss.

CHAIRMAN ROSENTHAL: So thank you all for being so patient, raising their hand. Doctors Hausman, White and LaRussa and then Ms. Celento again.

DR. HAUSMAN Thank you. Ethan Hausman. Some of the exploratory information we looked at, that didn't -- lost the level of confidence to making the review. We did a little bit of data mining on the issue of aggression. And it can fall out differently depending upon the age bands that we looked at. In the older pediatric age groups, there's very little data mining score because in the 15-year-old person that got listed on the report. In the younger patients, there were the five cases, so, the question about looking at the state and going there are so many reports. These are the reports in that age group. You have them. There aren't any more.

So if we go back and do something that is not 100 percent fair, when we look at the cover of cases that were confounded by multiple steroid administrations concomitantly, one might assume that these patients are not only getting off label use of the product that we're discussing today, but they're also getting multiple dosed with steroids, which it is, in fact, a concern to the committee, and should be, should be of concern to all the practicing pediatricians, nurse practitioners and everybody, but the issue is that when we get the reports

into AERS, one of the difficult things we struggle with when we look at safety signals is we don't always have, and we very frequently don't have, clean cases with exposures to a single drug for a very limited period of time with onset of adverse effect. That's not to say I have any answer to the question, I just want to bring that to the committee so they understand that we fully understand the complexities of the situation. That's how come we're here looking for guidance.

CHAIRMAN ROSENTHAL: Can you just summarize for -- you actually -- and I appreciate you went through each of the different reports again, but just help me to recall how many of the -- for how many of the reports was there concomitant use of another agent that was in the class of the two that are in combination. Let me put on my glasses.

I could have figured it out myself, but I would've had to have taken my glasses off.

DR. HAUSMAN: That's okay. One of the 2-and-a-half-year-olds had two steroids on board. The second one, the doctor for some reason that they didn't think it was related to the drug and they kept the drug -- the Dulera continued. One of the 4-year-old was on Dulera, pulmicort and Foradil, so two of them were on double doses at least multiple different medications of steroids. And so of the four under 5-year-olds, two of them were on multiple steroid medications. And there's no way to

peel these things out to do individual data mining because A) you pull out the cases where they're being double-dosed, that's not practical the way the computer system works. It can't be done and even if you do that you decrease the end. So what ends up happening is even if you take cases out, you wouldn't necessarily decrease the data mining score, you'd actually increase it because your denominator is shrinking. So it's -- so it's sub -- to parse it out even smaller than that would not be helpful to the committee.

DR. DURMOWICZ: Ethan, can you help us on that first one so we can understand.

DR. HAUSMAN: Yes.

DR. DURMOWICZ: Is that the one you're saying, this is the two-and-a-half-year-old who was --

DR. HAUSMAN: Dulera and Nasonex, the first one on top.

DR. DURMOWICZ: Yeah, and then it says they stopped the Dulera and the patient recovered. Concomitant medication review. So do we know that they stayed on the other drugs or do we know if we stopped all of them?

DR. HAUSMAN: Don't have the information.

DR. DURMOWICZ: Sorry?

CHAIRMAN ROSENTHAL: Yes, Dr. Reed has something to add to this.

DR. REED: I think we also have to consider with what you have brought up, that there's probably a good likelihood they were also getting an increase or overdose of the aerosol. Presumably at this age they're going to be using a spacer, recognizing that your ventilation will drive how much aerosol you take if you string a spacer and just continuing to breathe it in, they might have got a greater exposure. So not only are they doing two drugs, they might also be getting a greater exposure from the dose they got.

CHAIRMAN ROSENTHAL: So, okay, let's come back to this. I think it's an interesting discussion. Dr. -- let's keep coming around the table. Dr. White had his hand up.

DR. WHITE: You really have to help me out here just a second because I think part of the problem is understanding what waiver means. I'm new to this, let me make sure that I understand -- which is under PREA, if you want exclusivity, they come to you -- all together wrong, okay --

[laughter]

DR. DURMOWICZ: No, PREA is not exclusivity. PREAs required; so there is no exclusion --

DR. WHITE: Okay.

DR. DURMOWICZ: I should say, they could be given exclusivity --

DR. WHITE: Okay.

DR. DURMOWICZ: -- but the thing that triggered it, to be required, has nothing to do with exclusivity.

DR. WHITE: Okay, but under those requirements, do you only require a test -- testing -- in what you feel to be an appropriate population for use of these agents. So in studying the five to 12 age group, you had reviewed all the data, you felt that youth under the age of five is not safe, or otherwise not recommended. Is that correct? Is that a reasonable way to summate what you said?

MALE SPEAKER: There are about three or four different reasons which we look at on a PREA template and the company looks at with regard to deferrals and waivers. And the waiver it specifically is that one of them, which is an easy balance to check here is that disease doesn't exist in children.

DR. WHITE: Okay.

MALE SPEAKER: And COPD patients, you know, if it's just COPD drug that gets striked off and you just go away. The others are that it would be unsafe to give your population. The other are there better alternatives to treat them for disease than medication that is there. And usually only one box is checked, and we focus on one box, and I think that with regard to the box warnings and the LABAs was safety issue. But yet other issue that comes into play is there are better alternatives. Pushing the inhaled corticosteroid by itself

using the two drugs separately so you can type rate them rather than have one fixed in those combinations. So that's how it --

DR. WHITE: So in granting this waiver you consider the fact that there are other drugs available that are safer, A. B) you felt that it would be unsafe to use the combination. So you've already considered those things in granting waiver not to investigate it.

Now, in response to the concerns that, B, you should study it, I would say that the horse is out of the barn now. Do you have a drug which you feel is dangerous in this age group? We've looked at it, we've got data that it's dangerous. I don't know how you're going to ethically come up with a way around that other than go to the secretary of Health and Human Services and say this is a public health issue and have it reviewed by an all-star committee you can say, oh, well, it's important enough that we now have to go back and look at it. And if you look at the federal regs where researching children, you can't ethically do the study now, unless I'm wrong. I could be wrong. Anybody else have an opinion on that?

DR. DURMOWICZ: I'd like the division to comment also on the issue of just how we're going to measure the [unintelligible] under the five year old. I mean, isn't that one of the issue with the asthma drug where you're doing inhalers?

MALE SPEAKER: The efficacy in asthma trials is when you're talking about five and above --

DR. DURMOWICZ: Five and below.

MALE SPEAKER: Oh, below.

DR. DURMOWICZ: Yeah.

MALE SPEAKER: The efficacy is generally five and below is, except for a couple of medications including polacoid respials [spelled phonetically] which is a steroid, has been extrapolated from the five to 11 population. And safety, as you know, is not extrapolated.

DR. DURMOWICZ: So just one thing, because there are some concern about how you would actually measure some of these issues, is all I'm trying to get at.

DR. WHITE: Would you agree, though, that after we've raised the questions under subpart D, it would be difficult to design a study in which could then be carried out.

DR. DURMOWICZ: If you want to address that.

CHAIRMAN ROSENTHAL: So let me invite Dr. Skip Nelson up to a microphone.

DR. DURMOWICZ: I mean we do deal with this question as to how we do any of the LABA studies right now, actually, because of the -- of that box [spelled phonetically].

DR. NELSON: Yeah, yeah. This is Skip Nelson with the Office of Pediatric Therapeutics. And as you know to do a trial

in pediatrics where the risk is thought to be more than just minor increase over minimal risk, which this would involve, but the risks of administering the drug need to be justified by the benefit that you anticipate that child to receive and that risk-benefit balance needs to be roughly comparable to other alternatives.

Now if what you're saying is that the point people start using it off label, that the position, if you will, of studying it has been lost. Now I will at least propose that the kinds of questions you've raised today, perhaps even, raise that issue, I mean, that's the question. The difficulty here is a safety study is different, you know, from any other studies that you might want to do. It's not, you know, other than collecting them. If you don't think children should be on the drug, even if people are putting them on a drug, I mean, it's hard to then say we should do that study, but yet nevertheless clinicians are still using it, although in very small numbers. So, yeah, it might be difficult to do that study.

DR. DURMOWICZ: I think we could say yes it would be difficult [laughs] to do that study, I mean we've been in lots of conversations and just have to do LABA studies in general, now that they have black boxes, so, you know, would --

DR. WHITE: Just seems that what's happening is it's now out of the appropriate committee control because it's in the

hands of the individual, and we need to maybe write a stronger warning about use under the age of five in the labeling for this drug, based on the results that we have. Thank you.

CHAIRMAN ROSENTHAL: So, okay, there are a number of people that have had their hands up and we've actually been kind of keeping tabs on this. Ms. Celento, you're next up if you want the floor, no, okay. Dr. LaRussa.

DR. LARUSSA: So I hesitate to have a simple solution, but it seems like there's no way you can do the study and there's the way you should do the study. I don't know where this would fit best, but certainly if it were a contraindication -- if age were a contraindication to use the drug, that would send a much stronger message to physicians than just saying the drug is not indicated, it's not approved for use in children below a certain age.

So whether that goes into a contraindication or into the warning where you say there's some disturbing information about this age group and you can't dose correctly, or you put that in a contraindication. That sounds to me like a better idea than just saying that you can't use it or that you don't have any indication in the young age group.

CHAIRMAN ROSENTHAL: Okay, so, the next -- I'll just give you guys the next three so that you know who's on deck, who's on the hold. Dr. Wagener, you're up, and then Dr.

Wiefling and Dr. Towbin.

MS. CELENTO: Dr. LaRussa was before me.

CHAIRMAN ROSENTHAL: Okay. Then you're up next.

MS. CELENTO: So I think the suggestion that Dr. LaRussa made is a great suggestion. I'm not sure if there is a process for that, but I do want to say that you know there's something when I come to these meetings I question, you know, you have an entire network of pharmacies that's actually shrinking, as we know. There are very few community pharmacies left; it's CVS, it's Walgreens, it's Rite Aide, it's Wal-Mart. And, you know, I have two instances in the last year where something is prescribed for my son, and the pharmacist did not take the electronic order and just fill it. They stopped it and asked me questions and said, you know, in one case they don't carry it, they didn't order it automatically.

You know, the pharmacies have everything electronic, they stop and ask the questions. They have the consultations with the consumer while their standing at the desk. And I really don't understand why we're not using the pharmacy network, maybe potentially, in a case like this. And additionally, I think a much [unintelligible] physicians that are [unintelligible], but when -- Dr. Durmowicz, at the table said, you know, it's unconscionable that a practitioner would be prescribing this; hey, I'm not a practitioner, most of you are,

and, you know they get out the iPhone and look through the list of drugs that are available and what does someone's insurance cover, and, you know, there are a zillion things that can go wrong in the process of prescribing a drug, and there needs to be stronger warnings, the physicians need to be made aware. And I really thing we have to look at starting to use the pharmacy networks to really have the buck stop there. I think if we don't we're missing the point the completely, and we're missing opportunities to protect pediatric patients. Thank you.

CHAIRMAN ROSENTHAL: Dr. Wagener.

DR. WAGENER: So I'm one of those practitioners out there. And I'm going to follow on what Dr. LaRussa said and actually make a suggestion for the future. I see two issue of -- a couple of issues that are making this complicated. One is it's a combination drug, and I am in 100 percent agreement with what Dr. Durmowicz that this is not a drug that you would even propose studying in the younger children because it is a combination. You might propose studying one or the other of the drugs, but the combination is not something that you would typically study and it probably would be very hard to study anyway because of the low use.

The second though is there appears to be a safety signal in -- and I agree it's not huge but there -- almost -- four of the cases are in this young age group and what you

showed is less than 1 percent of the prescriptions from that age group. So when I start balancing those two points, I start saying that even though that's not really complications or adverse events, it's occurring in a group that's not using this drug very much and we're not seeing that adverse event commonly in other groups. So it raises concern for the younger child. It's a plausible signal. We've talked about both in steroid and a LABA. As far as the LABA is concerned there's a black box warning. It's getting to be a huge black box so people don't read it anymore but it's still a black box warning there, which is a good solution for that part of it. What I want to know is, is it conceivable that in the future if we have something that's waived under PREA, and if we've made a decision that it's a drug that's not appropriate or not expected to be used in that group, should the balance be that there'd be an automatic black box that says for children, this is a drug not expected to be used or not approved to be used under this age group? I know we said the FDA is doing exactly what I want it to do and that is they're making the logical decision with the company on a drug that shouldn't be studied, but in exchange for not studying it shouldn't there be something that tells the public that we really don't expect it to be used there, so that's why it's not going to be studied and we can't assure safety. We can't say anything about it. So I would suggest on a drug like this,

there be a black box developed that can be a group, you know, for all drugs in this category that simply says this drug is not studied under this age group because it's not expected to be used or it's not studied because we don't consider it safe to use it in this age group, and leave it at that.

DR. MURPHY: Well we do a fair number of waivers Dr. Wagener and I think, I would just say I didn't think we would want to say we're going to put a black box on our labels because as you've heard there're a variety of reasons. And so obviously if it's not to be used because some disease doesn't occur then somebody somewhere might still use it. We're not going to do that. You know, with FDAAA, if there's reason to waive it, it's related to safety. That's supposed to go in the label now, if we're waiving it for safety. I think what you're suggesting though is that we raise that to a higher level than just put it somewhere in the label. I mean, certainly if we do a major change and there has to be lots of discussion but I think from what I understand, what you're saying is that assuming it's a safety issue, even though we're required to put it in the law now, we wouldn't want to put it in the law, not just because it's required, but you're suggesting that that category that there be some higher level, you're suggesting possibly a black box, to make sure people are aware if the agency's thinking about safety in this product. Is that correct?

DR. WAGENER: Correct. I think the current -- most pharmaceuticals have such a long list of adverse events that issues like, you know, if there's an effect on growth get completely lost or -- but in this case, again, there's been a lot of good scientific thought about the decision to waive further studying a certain group. And I agree with your suggestion and that is if that decision felt that there's a safety reason not to study it in that group, then that ought to be prominently visible to the prescribing clinician because if you've made a decision there's a safety issue, they should be aware of that and it shouldn't be just some place in the list of many adverse events.

CHAIRMAN ROSENTHAL: Okay, so we have five people who have raised their hands, if I ignore the last two. So then we are, sort of, moving through the time window here. So Drs. Wiefling and Towbin, Towbin are next and then Joad, Mink, and Reed. Let's try and get -- let's see if after that if there really are any other questions or whether these five can address the questions of the people who, the latent hand raisers. So Dr. Wiefling.

DR. WIEFLING: The pressure's on. Okay, so [laughs] I wanted to say I totally concur. You took the words right out of my mouth about as far as being able to put a second -- a box that is more identified to the patient -- to the physician to

not use it. It seems to me, it strikes me that this is very similar to what happened with the SSRIs in adolescents, where they basically said, you know, if you use this you're pretty much an incompetent physician unless you really sought some additional, [laughs] some additional consultation. So I think that's thing one.

Thing two is if that for some reason is not palatable as far as black box warning, is there a way to take something that we already know is true and has been accepted that high dose, you know, high dose steroids in children is not considered to be safe. So that you're sort of giving it from a back door that way.

And then the last thing is I think getting to messaging through the electronic devices, so some of these websites and things like Hippocrates that physicians are using. I'm not sure what they draw from in order to pull their warnings, I mean because when you look at them it's not the entire label that you see, you only see like a couple of big things. So whatever it is that they're pulling from, whether it be the black box or a certain area of the label, it would be helpful to know that because this is something you would want to fall into to, that category so it gets picked up by the electronic software that's out there. And then, very last, I have kind of lost track of what you're going to ask us to vote

on, so I'm hoping we'll get back to that. Thanks.

CHAIRMAN ROSENTHAL: Okay, Dr. Towbin. We'll come back to that. Dr. Towbin.

DR. TOWBIN: So, to my mind there are three issues here and I concur emotionally to this, Dr. Wagener's comments. The first is, this is a real problem as a fixed-dose combination agent; and I think stronger language, perhaps in the usage and indications section, would make clearer that a combination agent like this should not be used in a younger population.

A second issue is that people may not be aware that other steroid agents in combination with this will push someone into toxicity, and so that would need to be made much clearer somewhere in the label and maybe in that usage section. And a third issue for me is that there's no neuropsychiatric adverse event in the label right now as far as I see it. So no one even knows to think about that in association with this agent. So language about that really needs to go into that section. Right now it just speaks to the cardiovascular effects and those were combined, the neuropsychiatric and cardiovascular, and maybe those need to be broken out and made much clearer.

CHAIRMAN ROSENTHAL: Thank you. Drs. Joad and Mink.

DR. JOAD: With regard to the not studying children under five, I think it's complicated. I don't know how you're going to say it's a real sense that it would be not safe for

them. It seems like you need to do -- if you're going to say it's not, I don't know how you're going to justify it. I'm curious to see how. I think it's a wonderful idea if you can do it, but I don't know. I don't know. There certainly are reasons to do combination medication in the young kids, particularly the compliance and adherence and everything to do that is much easier if you have a combination, if you're going to use both those drugs which I don't know that you should.

I wanted to concur with you about why don't we just add a concern about aggressive behavior to the list. The list, when I look at it, includes things that I, you know, many, many things and it would just be one more thing that you would add to the list that people could at least be aware that that might be what's going on.

And just a final thing, that people do end up using like medical steroids and lung steroids at the same time, and it's common -- I'm not sure. It's the same as when you add on other drugs together.

CHAIRMAN ROSENTHAL: Dr. Mink.

DR. MINK: I also wanted to echo what Dr. Towbin said, you know, there is reference on the class of drug, the section for beta agonists that can cause jitteriness and tremor. Well, in young children, that translates to irritability, and meanness, and aggression, and that's true for both steroids and

beta antagonists, and it appears nowhere on the label for this combination. But I think there is -- I don't know how much hard data there are, but there's certainly sufficient clinical experience for those drugs to -- to, I think, make many of us know that that happens.

And so one opportunity is to change the label to have a little bit more detail about each individual class of drugs. The second, as someone who prescribes a lot of things off-label because it's the nature of my specialty, you know, when I read a label that says -- or indicated for children 12 years of age and older, that's a very different message then, you know, use extra caution in children under such and such an age. And for one that I use commonly, diprotic acid [spelled phonetically], there is concern about, you know, fatal -- having toxicity, particularly in younger children. The data there are probably stronger then these data but still, you know, a negative message is very different than one that is just an absence.

And then, finally, is I do think that some kind of warning or concern is a good idea for this agent. Okay, thank you, and then Dr. Reed.

DR. REED: Dr. Mink addressed what I was going to bring up, and I concur with Dr. Wagener. I think we have a very unique situation here. Not only is it a combination drug it is, as Dr. Towbin mentioned, it is a fixed dose combination, and the

doses that’s there is inappropriate for this age group; thus, we should be proactive and we should add something to the label that states it’s inappropriate to be used because of this.

CHAIRMAN ROSENTHAL: And Dr. Ellenberg has just told me that Dr. Santana has a summary kind of statement.

DR. SANTANA: Well, yeah, I’ve been listening to this discussion and not disagreeing at all. We have to find a path forward here, and I think there's two issues. There's an issue that something needs to be done pretty soon. And so some information needs to go out to the community that although this is not statistically, you know, power or whatever, that there is a safety signal with this particular agent or combination of agents that's used in this very unique population, and that information needs to get out there while the agency then works on the more long-term solution, which is how do you then work with the sponsor, with the label, whether you want to or not do additional studies.

So what I would propose is that the agency -- maybe they need to tell us a little bit more regulatory tools they have to do this -- but there needs to be some immediate action based on the discussion today. And then there needs to be a more intermediate solution in terms of looking at the label, working with the sponsor in regards to how that label can be changed so that the information is there permanently.

CHAIRMAN ROSENTHAL: Okay, so I've been -- I hope I haven't missed anything but I have been trying to sort of follow some of these themes. One of the themes is that some information that could be transmitted from the agency to providers and prescribers regarding use of combinations along with the single agents that make up the combinations and the potential risk of toxicity when that prescriptive strategy is adopted. That's kind of a general concept of Protonix, since, you know, this drug, it's getting too complicated to think about that. But I think that the general idea is that when combinations and the single agents that make them up, they're both prescribed together, the likelihood of adverse -- of toxicity is greater --

DR. MURPHY: I just want to make sure that we -- because things get taken out of context -- we are talking about the younger age group because we've got a black box warning telling us not to use a single product, basically, okay, so I just want to make sure that --

CHAIRMAN ROSENTHAL: Yes.

DR. MURPHY: We keep saying that over and over again, just in our discussion about the problems with combination products. We're focusing on the younger age group -- just for all those people, actually, you know, take it out of context. I just wanted to --

CHAIRMAN ROSENTHAL: Yes, that is --

DR. MURPHY: -- we take that age thing into this discussion, okay?

CHAIRMAN ROSENTHAL: Around this product --

DR. MURPHY: Yes.

CHAIRMAN ROSENTHAL: -- around this product. But I actually think a more generic principal around prescription of -- and this is obvious to all people around the table, I'm sure, but, you know, I think a more generic point is that when combination drugs in general are used with the single agents that the likelihood of having -- of toxic side effects goes up. And I don't know how to -- I don't know how to transmit that in general. I think it's a principle that is one that people just keep in the back of their heads. But around this particular agent, I completely agree, we're talking about the younger age group.

DR. MURPHY: And it plays into the toxicity because the dosing issue --

CHAIRMAN ROSENTHAL: Exactly.

DR. MURPHY: Okay.

CHAIRMAN ROSENTHAL: So -- and actually, so the fixed dosing is another one of the things that I was going to call out, so -- so one of the comments that was made is that when -- given the fixed dosing, that the delivery of the single dose in

small children would always result in a dose that is considered too high. There has been a call for the addition of some neuropsych effects into the label, as there seems to be a lack of such -- of such -- of such in the label right now.

There was some discussion on the lack of efficacy data for these agents in the younger age groups, and similarly, there was -- that was linked with a discussion of the fact that there is safety signal, so -- and we've certainly dealt with that conundrum before, where we don't have good efficacy data; we do have some safety signals. So these are things that seem to have --

DR. MURPHY: And I was ask to remind everybody about the paper that came out showing the increasing as you went down in decreasing age, just in general for the LABAs.

CHAIRMAN ROSENTHAL: Can you speak up? I actually didn't hear what you said.

DR. MURPHY: I'm sorry, I was just asking to remind everybody about the fact we do have data out there on increasing risk appears in pediatrics with decreasing age of hospitalizations particularly. So just to remind everybody: This is not unheard of.

CHAIRMAN ROSENTHAL: And you're talking specifically with the use of long-acting data, I guess?

DR. MURPHY: Yes.

CHAIRMAN ROSENTHAL: Yes, okay, now, let me just ask everybody around the table were there other big themes around this discussion that we -- that we missed? Okay, so I think that probably summarizes things. Okay, so let's see what we are going to be voting on. So with the discussion -- I think -- I think that maybe what the agency is hearing from the committee is that people are not completely comfortable with the lack of recommendation of no labeling changes because of the -- this issue around adding some neuropsych adverse events to the label. Yes, yes, doctor. This is great. I am so happy that you guys are offering to summarize this. Dr. Rakowsky has a summary statement.

DR. RAKOWSKY: So a two-part question; first is that to return the post-marketing monitoring, continued monitoring, it looks like it's being done properly; and the second is that the committee will ask the division to relook at the labeling for children less than five and then report back after decisions were made. Is that going to summarize everybody's concerns or --

CHAIRMAN ROSENTHAL: Bless you. So let's -- we're going to reframe this question a little bit.

DR. MURPHY: I think you're going to have to, and I think, actually, it would probably be a good idea to break them out into the areas that you've -- to vote on what it is that you

would want the agency to change about the label, and how you are going to articulate that. But I think you're going to need to vote because it's clear that I think you need to do something with the label.

And I think, you know, as far as if you wanting additional reportings, then that won't just be routine work. We would have to then figure out what it is that we need to come back to -- it sounds like the number five, we're going to want to know. Like some other products, did their changes have an impact, you know, those sort of -- sort of things. So I think you would were correct, you'd want to reframe the question.

CHAIRMAN ROSENTHAL: So how about if -- let me -- let me ask -- let me ask that I ask the following questions. First will be whether or not to continue with the -- with whether we are going to continue labeling or not. For those who say no, if you could, following your vote, articulate briefly the kinds of changes that you might suggest to the agency and that might be related to the labeling issue. And similarly, if we ask a continued, routine monitoring question for those who say no, you could give us some ideas around what those changes would be. Does this seem reasonable for the table?

DR. SANTANA: Geoff, I have one question.

CHAIRMAN ROSENTHAL: Can you speak into the mic? Dr. Santana?

DR. SANTANA: So Dianne, is there something that the agency could do in terms of a professional health care letter until the labeling stuff is all figured out? I mean, I am still pushing that there's some immediacy to this while the label issues are being sorted out. Is there a regulatory tool that you have to let people out there know that there is some concern and what the concern is until it gets investigated fully.

DR. MURPHY: Yes, there is a couple of ways. One of which, as you know, is a health care letter --

DR. SANTANA: [affirmative], I would advocate for that while all these other issues are being studied and sorted out.

DR. MURPHY: We sometimes put stuff up on our med watch that relates to that. Is that a "Dear Doctor" letter? [inaudible] Yeah, yeah, I may have the wrong title for the -- so correct me on the title -- I'm still the dear doctor, whether it's a drug safety kind of question.

CHAIRMAN ROSENTHAL: So maybe a labeling question. I'll broaden it and not say just labeling but communication with prescribers. Okay, so the first question is: Do people feel that the agency should -- well, are people comfortable with not changing the label or the strategy of communication with prescribers and the -- and the alternative would be you -- you -- and so you would vote -- hang on a second --

MALE SPEAKER: [inaudible]

CHAIRMAN ROSENTHAL: Okay, we -- okay, we will do it then. I'm just going to go. So okay, let's do that then. So do people agree that the -- that the agency should continue monitoring for Dulera clinical trials in pediatric patients 5 to 11? All in favor of the current monitoring strategy for that age group, please raise your hands. Excellent. All opposed? Okay, let's go around the table and say your name. Dr. Reed.

DR. REED: Michael Reed, I voted yes.

DR. SANTANA: Victor Santana, I voted yes.

DR. RAKOWSKY: Alex Rakowsky, yes.

DR. WAGENER: Jeff Wagener, yes.

DR. TOWBIN: Kenneth Towbin, yes.

DR. KRISCHER: Jeff Krischer, yes.

DR. JOAD: Jesse Joad, yes.

MS. CELENTO: Amy Celento, yes.

DR. LARUSSA: Phil Larussa, yes.

DR. GLASIER: Charles Glasier, yes.

DR. MINK: John Mink, yes.

DR. WIEFLING: Bridgette Wiefling, yes.

DR. MOTIL: Kathleen Motil, yes.

DR. WHITE: Michael White, yes.

CHAIRMAN ROSENTHAL: Okay, thank you. So now the next question is: do you feel that the current labeling and communication with prescribers is adequate for children younger

than five? All that feel it's adequate, raise your hands. Okay, all who feel it is inadequate, raise your hands. And the extensions. All right, and now as we go around the table, please indicate your vote but also indicate if you felt it was inadequate what some ideas for the agency may render inadequate. Dr. White.

DR. WHITE: I believe there needs to be communication, probably posted on your website with regard to concerns of off-label use on children under the age of 5, and that needs to be negotiated with the company for some sort of warning recognizing the previous labeling, why it was put in place as well as our concerns based on the safety reports that we've received so far. And then I think there should be some negotiation with the maker regarding neuropsychiatric events that have been reported.

DR. MOTIL: Kathleen Motil, and I voted no. But I'm afraid I'm much less stringent on some of these requirements. I think a letter or some sort of communication would be appropriate concerning the use of combination products in a young child. But I -- and I think perhaps you could add some information to the label about some behavioral issues. But I hesitate to come down heavy because we have heard about two out of 2,000 instances where there was some behavioral change. The other two cases are clearly improper usage, and while everybody is blaming the physician, I can assure you that there are lots

of people out there who doctor shop, and one has no idea what goes on because people don't tell you even if you ask questions of them. So I am reluctant to be absolutely rigid about some of this.

I think the other scenario is for those of us who use steroids, and I certainly don't use one for pulmonary reasons but have other reasons to use them. There are times where we clearly tolerate aggressive behavior in younger children because we have the choice in what we are issuing when we have significant disease in a young child. So I voted no, but I am less inclined to be critical and harsh with the agency for placing all sorts of requirements.

CHAIRMAN ROSENTHAL: Dr. Wiefling?

DR. WIEFLING: Dr. Wiefling. I did vote that it was inadequate, and I value the support of a drug safety letter that goes out know, letting physicians of the risk of off-label use of the combinations meds in children under 5, and hypersteroids. And I am also in favor of changing the label so that it is more reflective in the fact that there have -- you know, that less than 5 is found to be unsafe.

DR. MINK: John Mink, I voted no. A couple of suggestions: We know there's substantial evidence neurocritical steroids and the others can cause aggression and irritability in a dose-dependent manner, and I think that that's something that

belongs in the label somewhere, even though it wasn't directly tested in this product. And then furthermore, I think some language specifically advising against using this in children below the age of 5.

DR. GLASIER: Charles Glasier, I voted no. I concur with most of the comments. I think there should be some sort of warning label -- warning label that goes out, and some change to the label which is reasonable and not too harsh, so...

CHAIRMAN ROSENTHAL: Dr. LaRussa.

DR. LARUSSA: Phil LaRussa, and I also voted no. And I would suggest adding to the label precautions, exceptions stating about the inappropriate use of this fixed dose combination in the 0 to 4 age group because of the difficulties in appropriate dose, in the addition of the neuropsych symptoms that I've been seeing. And I would also support a letter going out to the -- to a doctor, letting them know.

MS. CELENTO: Amy Celento, and I voted no. And I will go with Dr. LaRussa's same comments.

DR. KRISCHER: Jeff Krischer, I voted no, and my comments have already been stated.

CHAIRMAN ROSENTHAL: Dr. Joad.

DR. JOAD: I'm Jesse Joad. I would like to see aggressive behavior added to the label, and I agree with the comment that it's not a terrible side effect, I mean, it's one

for which you all discontinued the drug or cut the dose or something. I just want people to be aware of -- that that's a possible thing might happen and they should act appropriately.

And then I feel uncomfortable about jumping on the bandwagon that we know this is ineffective and unsafe for children under five. You may all know something I don't know but it seems that should have considered discussion with data presented that says that's the case before we -- you know, dosing doesn't necessarily make sense because children dose themselves with smaller kinds of volumes, and you don't give less Albuterol to a four year old than we do to a 20-year-old football player. So just jumping on the dose being incorrect because it's the same as an older person probably doesn't make sense. I just think it needs more thought and consideration, and if it's so, then I would love it to be on the label.

DR. TOWBIN: Charles Towbin, I voted no. I think there are two label changes that I would speak to. One is in Section 5-11, where we now combined their psychiatric and cardiovascular events; I would to see that separated so that CNS events really receive their own billing when people know to look there. And we could list things like irritability, aggression, behavior changes, and so on.

And I think in the other -- given that this fixed dose combination has plausible concern for safety in children under 5

within the usage and indication section in the same way that we say it's not indicated for bronchospasm, we could say it really isn’t appropriate to use this fixed dose combination in children under 5.

I think one other comment is looking at the questions here, the one related to continued monitoring the ongoing Dulera clinical trials in patients 5 to 11 years in age. I think we are awaiting that data to come in, and my hope is that neuropsychiatric side effects or ill-effects are part of what's being monitored in that, given the signals that we’ve seen here and how it wasn’t in the label originally. We may not be asking people about that, and so we want to be sure that was part of what was being ascertained. And the other is if the data could be broken down so we can see data from the 5 and 6-year-olds broken out from the older children because that might give us some sense about whether the younger children are more vulnerable. Thank you.

DR. WAGENER: Jeff Wagener. I agree with Dr. Towbin’s point that -- first, I voted no. I agree with Dr. Towbin’s point that there should be an addition of the neuropsychiatric adverse event section, at least mentioning children and aggressive behavior. I also think there should be an addition of some form of warning regarding its use in less than 5-year-olds. The location of that, I think, is -- depends upon with

the FDA would like to do.

I would also just make a comment: I do not agree with sending out some form of letter. Although I think there's is a small signal of something in these younger children, I don’t think it's to the degree that it warrants a special notification of all physicians in the United States to avoid the use of this in that age group. So I would look at changing the labeling as the principal way to address this potential problem.

DR. RAKOWSKY: I'm Alex Rakowsky, I voted no. In regard to the label as Dr. Durmowicz, the lesser half of the Durmowicz as he referred himself, has mentioned there have been multiple findings and multiple communications with the sponsor, so I don’t think it's under the offices for this committee to state which part of the label it should be put in. But I think they're aware of our concern, and then just to work on the label.

Once the label changes have been made, then I think that communication could be sent out, including the pharmacies, as Amy mentioned, since I think that's where a lot of the rub is going to be in terms of a pharmacist questioning, you know, were you aware your child may be too young.

DR. SANTANA: So this is Victor Santana, and I voted no. And my explanation to points of this discussion is that I do agree that sections of the label, as been previously eluded

to, need to be revised to reflect a population that potentially has greater safety concerns compared to the other populations and the evidence that has been studied. Whether that goes with safety, or the warnings, or, you know, the agency is the expert on where that goes best on the label.

I do think that we've spent an hour here discussing an issue, and I think that some communication to health care professionals needs to be directed to make them aware that this issue is being discussed and will be addressed. The content of that, the detail of that, I think the agency has the expertise to do that, but I do think a health care professional letter should go out.

DR. REED: Michael Reed, I voted no. In thinking about the limitations of data that we're all familiar with, in a one-hour discussion, I feel it is appropriate to modify this label. In that, just simply reminding the practitioner that this drug is not labeled and should not be used in patients under the age of 5, as -- and it could comment that there is some signals or some suggestion of this. To me, it is taking exactly as someone had brought up of what we had been doing and being proactive in getting information out.

I also believe it's having one of your communications -- you know, I get one multiple times a day by email -- I think it could be easily put together, again, reminding clinicians

this drug is not indicated for use in the age group, and then we can move forward. I do feel though the fixed dose combinations Dr. Towbin brought up is not appropriate to be studied in this group, and that we've gotten our communicate out.

CHAIRMAN ROSENTHAL: Okay, thank you. And then the -- the last part that we had discussed in the nice summary one of my colleagues was regarding the issue of routine monitoring of the younger-than-five group. And so just to remind people that routine monitoring is a fairly robust process, and if -- so let's go around the table and vote of how many people are in favor of returning to routine safety monitoring of Dulera in the less-than-five age group. We've answered the question for greater already. All in favor of routine monitoring in the less-than-five-year age group. Any opposed to that approach? Okay. And you -- yes?

DR. WAGENER: Dianne, I have a quick clarification. Routine monitoring, does that affect when this will come back to the committee?

DR. MURPHY: Yes. Routine monitoring per what it is, but if you don't ask for it to come back to the committee, or you don't have any reason for it to come back to the committee, it does not come back to the committee. Unless it's trigger, as you heard in one of the earlier products, HIV products in that younger age group, there -- they've got those studies out there

with labels that will trigger that. But this kind of labeling would not. If not a new population, it's not a new indication, it wouldn't trigger coming back to the committee.

So I -- it does affect whether you come back or not. You have to ask for it to come back, otherwise it does not come back, unless they find something -- yeah, unless they -- but that’s basically, you know, when they decide how and to whom it comes back to.

CHAIRMAN ROSENTHAL: So let me just clarify. There are some -- some regulatory triggers that would result in a requirement that the product would come back to the committee, and then there -- there are also some things that could come up just regarding the new findings, new issues where the division may request that the product come back before this committee because of something that this committee might have in helping their division to deliberate on the issue, okay, yeah.

DR. MURPHY: But they could decide to bring it back to different committee.

CHAIRMAN ROSENTHAL: Yes. So Dr. Wagener and then Dr. Towbin.

DR. WAGENER: So would it be reasonable for us to offer an amendment to our proposal requesting that -- I’m impressed that the committee has started asking questions and has concern here. Is it reasonable to say -- to ask the FDA to

bring back this product within the next three years to give follow-up on what their concerns were that were expressed here.

CHAIRMAN ROSENTHAL: We can -- we can ask for that. What would be the reason for asking for that?

DR. WAGENER: I'm just impressed that we have spent a lot of time discussing, and we come up with some suggestions, and this committee doesn't have the authority to mandate, and given the concerns expressed, it seems appropriate to ask the FDA to come back with a statement of what they've done, and with their adverse event follow-up has been for the next few years. And I think in three years, there would at least be data. It may not be the same, but it would answer the committee's concerns.

CHAIRMAN ROSENTHAL: Now, we've talked about this for an hour and half. Several people have pointed that out. There have been times when we've talked about long-acting beta agonists and the pediatric population for days. And, so, you know, it occurs to me that long-acting beta agonists come up as a class for discussion not infrequently on this committee.

So, I'm wondering whether some -- well, first, I'm sorry. I'm not remembering whether there is a plan in place already to review long-acting beta agonists at some point in the future based on the previous meetings.

DR. MURPHY: There's a -- there are trials that are

going to be conducted, but they will be a long time coming. I mean, that's my understanding. Right?

CHAIRMAN ROSENTHAL: Dr. Towbin?

DR. TOWBIN: Yes. In fact, this speaks exactly to the question that I wanted to raise, which is what is the timetable for those trials? Dr. Hausman has been making eye contact with me, or me with him, so I bet he has the answer.

DR. HAUSMAN: 2016 is when the studies come in. So the presentation's impact would be at some point after that.

DR. MURPHY: Five to six years.

CHAIRMAN ROSENTHAL: Okay, Dr. Wagener?

DR. WAGENER: Just a clarification, I'm actually much more concerned about the steroid, not the long-acting beta-agonists. I think the steroids is what's producing this and it's a much bigger issue.

CHAIRMAN ROSENTHAL: Okay. So prior to this part of the discussion, we actually had voted on returning this combination product to routine monitoring for children younger than 5. And maybe people can give me a sign about whether we need to re-vote, or whether we should -- okay.

DR. MURPHY: We voted already --

CHAIRMAN ROSENTHAL: Dr. White says no.

DR. MURPHY: Okay, so the -- we voted already. It sounds like we're in the midst of finalizing the vote, right?

CHAIRMAN ROSENTHAL: Well, what happened was we voted, and then the clarifying question.

DR. MURPHY: And that caused some lack of clarity.

CHAIRMAN ROSENTHAL: That's right. Right, so imagine --

DR. MURPHY: So maybe because there is that question, maybe that you need to add a question, which is how many people would like to recommend that there be follow-up to this committee, okay? And there are these other things we would like to say, that would be part of the follow-up.

CHAIRMAN ROSENTHAL: Okay. So we voted on the monitoring process, and there was, at least by a show of hands, we'll go around the table and have people call out their vote, but by a show of hands, there was a unanimous vote that we should continue routine monitoring the younger age group.

The next part that came up was this issue of when the committee wanted to hear an update regarding new information and new safety signal. So as we go around the table and indicate our votes verbally, if you could please just indicate whether you'd like to have this product come back to the committee as it normally would, using the regulatory and other potential triggers, or whether you would like it to come back to the committee at some earlier time, that might be productive.

So, one other thing that I'll just throw out is that

asking to have these products come back to the committee too soon is never fruitful. So let's go around the table and do that once, and then Dr. White, will you get started for us?

DR. WHITE: I voted yes for returning to routine review for 0 to 5 years of age, and I think it should come back to the committee when the FDA has useful information for review.

DR. MOTIL: I voted yes to return to routine review and agree: When the agency feels has data, return it to us.

DR. WIEFLING: This is Bridgette Wiefling, and I agree with returning to routine monitoring until the agency makes a decision on this product to come back.

DR. MINK: I agree with both, although, let me add that I think five or six years is too long.

DR. GLASIER: I voted yes for the continuing review, and also to come back to the committee after an appropriate time period.

DR. LARUSSA: I vote yes to return to routine monitoring, and I would suggest that a reasonable period of time after the labeling changes have been incorporated might be a good time to look.

MS. CELENTO: This is Amy Celento, and I voted yes to return to routine monitoring, and I'd like to set a timeline of 24 to 30 months.

DR. JOAD: Jesse Joad, I voted yes for routine review,

and when it's fruitful.

DR. KRISCHER: Jeff Krischer, I also voted for routine review and to come back when the FDA feels it has appropriate information to share.

DR. TOWBIN: Kenneth Towbin, I voted for returning to routine monitoring. Of course, I look forward to hearing the results of the studies after they return in five or six years. Also, I trust the agency will let us know if there's a signal for them, and the routine monitoring would show it.

DR. WAGENER: Jeff Wagener, I voted yes. And I'd like to ask the FDA to come back in the next three years with a report on what their actions had been.

DR. RAKOWSKY: Alex Rakowsky, I voted yes, and hard to come up with a time frame, but there is information that raises more suspicion about the signal to come back.

DR. SANTANA: I voted yes to return to routine monitoring, and just offer the suggestion that I think what we're asking is when there's additional information that's pertinent for us, for the younger age group, to be brought for further discussion and information. One context in which that could be used, when the studies were the 5 to 11 year group, again, then that information can be presented because it would put it in some sort of context. But that's a suggestion.

DR. REED: Michael Reed, and I voted yes. I concur

with Dr. Santana, with what he had to say, though I would like the agency to return with the underage group, the surveillance data, earlier kind point that you choose, but earlier before the completion of the 5 to 11 age group studies.

CHAIRMAN ROSENTHAL: Okay, thank you. We're about a little over a half an hour behind right now without our break. But it seems like we should take a break, so let's -- I have 12 minutes after 4:00. Let's come back at 25 after 4:00, and we'll resume with a discussion of Nasonex. And I'd like to remind everybody to please not talk about the proceedings in the meeting outside the room. And to Dr. Durmowicz, thank you very much for helping us through this conversation.

NASONEX (MOMETASONE FUROATE MONOHYDRATE)

STANDARD REVIEW OF ADVERSE EVENTS

CHAIRMAN ROSENTHAL: All right. Time to wander back to your seats. All right. So for the next -- the next product is Nasonex, and Dr. Hewitt is recused from this discussion, and Dr. Durmowicz will, again, be presenting this, and there may be some of the same issues. I think if some of the same issues arise, then we can acknowledge them, and maybe not display them to the degree that we know that we can if we want to. Okay, so Dr. Durmowicz.

DR. DURMOWICZ: All right. So moving on to another mometasone containing product, Nasonex, and again, my presentation will follow the following outlines, similar to other safety reviews, and this safety review is actually the result of two labeling changes; therefore, I'll be discussing the clinical studies of Nasonex for the treatment of nasal congestion associated with seasonal allergic rhinitis, as well as the studies of Nasonex and the treatment of nasal polyps in pediatric patients, and I'll discuss both of the labeling changes that occurred.

Nasonex is a nasal corticosteroid marked by sharing. It was originally approved in 1997 for the prophylaxis and treatment of the nasal symptoms of allergic rhinitis, in

patients 12 years and older. The original market approval was in October, 1997, and is currently indicated for the treatment of allergic rhinitis in patients 2 years of age and older, treatment of nasal congestion associated with seasonal allergic rhinitis in patients 2 years and older, prophylaxis of seasonal allergic rhinitis in patients 12 years in age and older, and treatment of nasal polyps in adults.

In May, 2010, the indication for the relief of nasal congestion associated with seasonal allergic rhinitis was approved in adults and pediatric patients 2 years of age and older, and in January, 2011, findings from a trial of Nasonex and the treatment of nasal polyps in pediatric patients were added to labeling.

The safety and efficacy of Nasonex for the treatment of nasal congestion associated with seasonal rhinitis or established based on data from three clinical trials evaluating Nasonex in over a thousand patients 12 years and older, in which over 500 patients were exposed to Nasonex. The efficacy in nasal congestion in patients two to 11 years was established based on extrapolation of efficacy from patients 12 years and older, and safety and efficacy were supported by studies of seasonal allergic rhinitis in patients 2 to 11 years. No new safety signals were identified in the clinical trials.

The study evaluating the use of Nasonex in the

treatment of nasal polyps in pediatric patients was a single four month study in 127 patients, 6 to 17 years. The result of the trial did not support efficacy, however, the adverse events were similar to the adverse advents reported in patients 18 years of age and older, and were consistent with the known safety profile of Nasonex in pediatric patients.

The labeling changes that occur as a result of a nasal congestion indication approval occurred in May, 2010, and are briefly summarized on this slide. At this time, a PLR conversion was also approved. The indication was added, dosing for patients 2 to 11 years, and 12 years of age and older were also added. The adverse events that occurred more frequently in patients treated with Nasonex compared to a placebo where added to Section 6.1, and this section notes that the overall safety profile was the same as in other allergic rhinitis trials. The clinical studies section of labeling was also changed to include data from the three clinical trials.

The labeling, in response to the pediatric nasal polyp study are summarized on this slide. Section 8.4 was updated to briefly describe the nasal polyp study and states that the trial did not support efficacy. Labeling notes that the adverse events were similar to those seen in adults.

Relevant safety information in labeling is summarized on the next two slides. Nasonex has five warnings and

precautions. The local nasal effects include epistaxis, candida infection, nasal septum perforation, and impaired wound healing. The adverse reactions section of labeling provides a clinical trial experience in patients with allergic rhinitis less than 12 years and those 12 years and above. The pediatric use section provides information again, about reduction in growth velocity and the pharmacodynamics subsection of the clinical pharmacology section describes the adult and pediatric studies evaluating adrenal function.

So, moving next to the drug utilization data, this graph provides a number of patients receiving prescription from the U.S. outpatient regional pharmacies for Nasonex, based on the patient age for the years 2000 to 2011. So, this one's working. The number of patients increased from approximately 4.2 million patients in the year 2002 up to approximately 5.8 million in 2007, and then has decreased again to approximately 4.4 million patients in the year 2011, and my understanding of this is because of a competitive product that's on the market now.

Over the time period examined, the majority of patients were age 18 years and older, which is this purple line here, followed by patients 2 to 11 years, which is the yellow line with the triangles. Then, patients 12 to 17 years are represented by the aqua line, and the pink line, which is kind

of below the maroon line, is the patients zero to 1 years.

This table provides the number of prescriptions dispensed from U.S. outpatient retail pharmacies and the number of patients receiving the prescription for Nasonex, based on the patient age for the year 2011. The far column on the right represents the unapproved age group, and I've got the pediatric age group in kind of a light blue-aqua. During this one year period, over eight million prescriptions were dispensed to over four million patients. Pediatric patients received approximately 25 percent of its number of prescriptions dispensed and were approximately 30 percent of the total number of patients.

So, looking across the pediatric age range, there are approximately two million prescriptions dispensed across approximately 1.3 million patients in this one year period. Looking at the diagnosis for which Nasonex is prescribed, allergic rhinitis and chronic sinusitis were the top diagnoses for all age groups.

Looking at the specialties that are prescribing Nasonex, the pie chart on this slide shows the number of prescriptions dispensed for Nasonex by the top prescribing specialties from U.S. outpatient retail pharmacies, over the years 2002 through 2011. As you can see, general practice, family medicine, and doctors of osteopathy was the top

prescribing specialty, followed by internal medicine, pediatrics, and then EMT.

Moving to the safety review, the AERS database was searched for all reports of adverse events, serious and non-serious, over the 10 year period, from January, 2002, up to December, 2011. The AERS reports -- the AERS database contained 841 reports for Nasonex, 103 of these were pediatric reports, which represents about 12 percent of the total reports. Ninety-seven of the reports were serious and there were three reports of death. The reports of death and the unknown age range were reviewed and a pediatric patient was identified. However, this was later determined to be a duplicate report.

This slide summarizes how the cases were selected. We started with 98 serious adverse advantage reports, which included the 97 serious outcomes plus the age unknown pediatric death. Six reports were excluded, as they were duplicate reports. Of those 92 unduplicated reports, there were three reports excluded, secondary to a medication error, a report miscoded as pediatric, and a report that was not an adverse event. This left us with 89 identified reports to review.

So, looking at some of the characteristics of the serious pediatric adverse event reports, you can see that there were four reports of in utero exposure, four reports in the unapproved age group, and then the remainder of the reports were

all in the approved age group. The range of the dosing was from 50 to 200 micrograms. So, the maximum approved dose for Nasonex use and the duration of therapy, which was reported on maybe a little less than half the patients, was about 27 days, with a range from 1 to almost 2,000 days.

This slide summarizes the serious adverse events by organ system, and I will review the reports in subsequent slides. The unlabeled events will be labeled. Although the main focus of review was pediatric deaths and pediatric reports of serious adverse events, other events of interest associated with nasal steroid use were evaluated, but no reports were identified.

So, looking first at the two fatal events on both of these cases were confounded by concomitant medications and other preexisting, or coexisting, morbidities. The first is a 7-year-old boy with a fatal asthma attack after starting Lansoprazole. Additional medications other Nasonex included a long acting beta agonist steroid aerosol, which is a product labeled for asthma related death, and Cingulair.

The second report was of a 9-year-old boy who, per the report, died to dizziness, dysemia, dysphasia, which means difficulty standing, dysemia, muscle -- excuse me, dysphasia, arm movement disorder, gastric dilation, and increased weight. This patient was on several medications labeled for use for

psychiatric disorders, and many of these medications are labeled for similar adverse events.

Moving on to the other serious adverse events, there were 27 central nervous system events, which were broke down into neuropsychiatric events, seizures, and general CNS events. There were six reports of the neuropsychiatric events. There were 12 of those. Nine of those were unable to assess the causality due to preexisting medical disorders, and common exposure to steroids, and insufficient clinical information. And I provide the remaining reports, and we'll discuss those now.

There were three reports of behavior problems. The first was a 2-year-old with irritability and temper tantrums after one week of Nasonex use at bed time. The events resolved with discontinuation, but recurred with reinitiation, and then it resolved again with discontinuation.

The second report is a 7-year-old boy who developed behavior problems and trouble swallowing after starting Nasonex. A psychiatric evaluation was not helpful in determining the cause of the behaviors, which improved with Nasonex discontinuation. Restarted Nasonex resulted in recurrence of the behavioral issues.

The 10th report was a patient who reported multiple psychiatric symptoms, and this was a 6-year-old male with depressed affect, suicidal thoughts, anxiety attacks, and

hypochondriac behavior for five weeks after discontinuation of Nasonex. This patient was also on montelukast, which is labeled for neuropsychiatric events, as well as Xopenex, which is labeled for anxiety and nervousness, and the two remaining neuropsychiatric events on this slide, we were unable to assess the causality of these.

There were nine cases of seizures reported, five of which were compounded by a history of seizures. This slide provides a summary of the four reports in patients without a prior history of seizure. There was an 8-year-old male who was said to have an anxiety attack, which included convulsions, hallucinations, dilated pupils, and loss of body control, and night terrors, and these events occurred for five times in one night. This patient was also on Cingulair, Zyrtec, and occasionally Protopic. The Nasonex was discontinued and at the time of the report, these events had not reoccurred.

There was a 9-year-old male with headaches and a possible seizure, after one year of intermittent Nasonex use. The Nasonex was restarted and these events recurred, and the patient was referred for an evaluation by neurology.

There was a 4-year-old male with an episode of hyperactivity, followed by staring, disorientation, and no engagement in conversation, 30 minutes after day two of Nasonex. The patient was evaluated in the emergency room and their

examination was normal. Nasonex was not thought to be the suspect drug and the patient was referred for a neurology evaluation.

And a last case was a 7-year-old male who had suspected epilepsy and a planned EEG, who developed a prickle in the mouth, stuttering incomprehensible words after one month of Nasonex use.

Looking at the general central nervous system events, there were six reports. There were two reports of memory loss, which is an unlabeled event. The first in a 13-year-old male with disorientation, nervousness, and memory loss during treatment for sinusitis and fever, with Nasonex, Azithromycin, and sodium dipyrone. The Nasonex was temporarily discontinued, and the disorientation and nervousness resolved, however the memory loss outcome was unknown.

And a second case was a 16-year-old male with a 24 hour memory loss, while using Nasonex and Azelastine, and there was minimal additional information provided with that case. The remaining four central nervous system reports were single cases.

We received 11 vision reports, 11 disorders of vision reports. Review of these events identified three specific unlabeled events, intracranial hypertension, Papilledema, and temporary vision loss. From looking at the Papilledema cases, there were four, and three of these reports also reported

intracranial hypertension. The first was a 5-year-old female with fever and sore throat, who developed headache, blurred vision, and vomiting. The patient was diagnosed with Papilledema and intracranial hypertension, and this patient was on concomitant medications, including beclomethasone inhaler, Salmeterol, Clarithromycin, and Desloratadine.

The second patient was a 13-year-old female with eye pain, who was diagnosed with Papilledema and benign intracranial hypertension, and this patient was also on Desloratadine.

There was a 12-year-old male on somatropin, which is a product labeled for intracranial hypertension. He was diagnosed with Papilledema and subsequently was psuedotumor cerebri. The somatropin was discontinued, and the Papilledema resolved.

And the last case was a 16-year-old male who had kind of a somewhat complex history of a tick bite, encephalitis, and eye surgery, was on Nasonex and was diagnosed with un-sharp papilla. The Nasonex was discontinued, however the Papilledema continued. The remaining vision disorders, except for the one report of temporary vision loss, are all labeled events.

Moving on to the respiratory events, there were 11 reports. All of these reports were labeled. There were two reports each of five different events, and then one report of cough. The hypersensitivity events were labeled, except for two single case reports. There was one report of glosodinia, and

one report of tachycardia. The gastrointestinal events had three unlabeled events, specifically constipation, red stools, and cramps.

There were five reports of hearing disorder, the unlabeled events for hearing loss and tympanic membrane perforation, but that report was secondary to trauma. There were three metabolic events. All of these were unlabeled events. There were two reports of weight gain. The five year female had a 26 pound weight increase over an unknown time period, while on Nasonex. The Nasonex discontinued, but was restarted, and resulted in a four pound weight increase in four weeks. This patient was also on Desloratadine. And there was also a 10-year-old female with a 10 pound weight gain over an unknown period of time, and one patient who had hyperglycemia for three days.

There were three musculoskeletal events. These were all labeled events. Interestingly, there were two cases of growth retardation, and both of these cases were confounded by concomitant inhaled steroids, one for two years and one for four years, and they did -- these patients did have laboratory values consistent with adrenal insufficiency.

The renal and hematologic events were unlabeled events. There were two reports of elevated hepatic enzymes. A 5-year-old male who was admitted because of elevated enzymes,

who was also on loratadine, though no additional details were provided for this case, and a 23-month-old male with an elevated ALT and AST, who was also on cetirizine and tetrahydrozoline. There was also one report of proteinuria in a girl who had been on Nasonex for one month.

There are two reports of infection, infection being a labeled event. The three remaining serious miscellaneous events were labeled single case reports of bradycardia, heart attack, and lack of affect.

So in summary, our safety review identified 89 foreign and domestic serious adverse event reports, including two reports of death over a 10-year period. For the utilization data, approximately two million Nasonex prescriptions were dispensed approximately 1.3 million pediatric patients in the U.S., in 2011. The majority of the reports were labeled events in single case reports. We found that interpretation of unlabeled events was limited by conflicting information, incomplete case descriptions, and underlying medical disorders in concomitant medications. No new safety signals were identified. The agency recommends continued, routine post marketing, monitoring, and would be interested in your -- if you concur. I'd like to thank the following individuals for their help with the presentation.

CHAIRMAN ROSENTHAL: Thank you, Dr. Durmowicz.

Questions for Dr. Durmowicz regarding Nasonex? All talked out, are we?

[laughter]

DR. WAGENER: Actually, this is unrelated to Nasonex completely, but when you look at the numbers of the reported events, there's the adult, the pediatric, and then unknown age group. Who looks at the unknown age group?

DR. DURMOWICZ: Well, I'll defer to the OSE people. We always try to look at the unknown age group for deaths, and then depending if we're looking for a particular signal, but I'll defer to Ethan.

DR. HAUSMAN: Yeah, hi, Ethan Hausman. Well, it depends upon the nature of how many reports there are. We always make -- no, we always assess the unknown age deaths to see if there are pediatric patients. We, basically, convert and file, and do a string term search for popular ways to talk about children, and then that's how we identify those reports. For the serious, but non-deadly events, it actually becomes an issue of how many reports there are. In some cases there are thousands and we can't make it through, so we have a working cutoff that we assess when there are under a certain number of reports, we do the string terms. Then, we do the search again for the non-lethal, serious adverse events.

CHAIRMAN ROSENTHAL: All right. We had some other

hands. Shall we vote? Okay, that's an enthusiastic head nodding that I'm seeing. All right. Can you take us back to Slide 28, please.

DR. DURMOWICZ: Sure.

CHAIRMAN ROSENTHAL: Given that there are no new safety signals, the FDA is recommending we return to routine, post-marketing monitoring. Does the committee concur? On in favor, please raise your hands. Any opposed? Any abstentions? Okay, Dr. Reed, will you just state your name and vote.

DR. REED: My pleasure. Michael Reed, I vote yes.

DR. SANTANA: Victor Santana, I vote yes for routine monitoring.

DR. RAKOWSKY: Al Rakowsky, yes.

DR. WAGENER: Jeff Wagener, yes.

DR. TOWBIN: Kenneth Towbin, yes.

DR. JOAD: Jesse Joad, yes, but I'm not sure how much is related to the long discussion we just had, but it did look to me like there were some behavioral issues with new challenge, and then there was six that weren't described, and I don't feel totally comfortable with that, but given the denominator is so much bigger, I vote yes.

MS. CELENTO: Amy Celento, yes.

DR. RAIMER: Sharon Raimer, yes.

DR. LARUSSA: Phillip LaRussa, yes.

DR. GLASIER: Charles Glasier, yes.

DR. MINK: Jonathan Mink, yes. A brief off the cuff calculation for those -- if you look at the series of adverse events per person receiving the prescription, it's pretty rare. It's 5 per 100,000 for the 12 to 16 year olds. It's 6 per 100,000 for the 12 year and under [spelled phonetically], but it's 1 per 10,000 for the under two years old. So we continue to see that children who are given these prescribed below the age range for which is noted, seem to be of higher risk for having problems.

DR. WIEFLING: Bridgette Wiefling and I vote yes.

DR. MOTIL: Kathleen Motil, yes.

DR. WHITE: Michael White, yes.

CHAIRMAN ROSENTHAL: Thank you, Drs. Durmowicz, et al, and everyone else who's been involved in this particular discussion and presentation.

JUSTIFIED ABBREVIATED: RATIONALE PROVIDED

TAXOTERE (DOCETAXEL)

OMNARIS NASAL SPRAY (CICLESONIDE)

NATAZIA (ESTRADIOL VALERATE AND ESTRADIOL VALERATE/DIENOGEST)

PROTONIX (PANTOPRAZOLE)

QUESTIONS AND RECOMMENDATIONS

CHAIRMAN ROSENTHAL: So, now we're going to move on to the justified abbreviated reviews by Dr. Cope. There are four products that we will be talking about, and please join us in accepting this small celebration on the screen.

So, we will have surpassed our 200th safety review today. So, congratulations and thank you all on the committee for your participation in this important milestone. Now, Dr. Hewitt can return for the discussion of these products. Dr. Ramier, we need to ask you to recuse yourself for the discussion of Natazia, Protonix, and Taxotere. All right. Dr. Cope, the floor is yours.

DR. COPE: Yes --

CHAIRMAN ROSENTHAL: Hang on. Let me introduce you formally. Dr. Cope is a person who needs no introduction, but I'll introduce her anyway. She's been with the FDA for eight years, working first with the Center for Devices and

Radiological Health on pediatric device related issues, and then the Office Pediatric Therapeutics, to focus on pediatric safety for FDA regulated products. Dr. Cope's clinical background is in adolescent medicine, juvenile pediatrics, and epidemiology, and after several years of clinical and academic practice, she received an MPH in epidemiology and biostatistics, and Dr. Cope has helped us in so many ways as we have navigated the waters of pediatric safety reviews. I want to just acknowledge my appreciation for that. So, Dr. Cope.

DR. COPE: Great. Thank you, and I know we're behind schedule, but I really did want to take the first two slides, I really wanted to thank everybody and echo all of the hard work and dedication that you've all given over the past several years, and some of you newcomers, to pediatric safety issues related to FDA regulated products. And actually, some of you may have been here in June of 2009, and at that time, I had a slide of just one of those flashes of fireworks, because we actually had reached 100 products that had had mandated safe reporting, and so that was in '09.

So, the legislative history is that we started this in '03, and it was June '09 that we had just reached 100 mandated safety reviews. So, if you think about it, the legislation has increased everyone's workload, and so we have now, just in the last three years, gone over another 100 mandated pediatric

safety reviews. So, I do thank you. We all thank you. I put here, just this is our website with a link above, and I just want to remind folks that if you go below the pictures, there's a second bullet called Safety Reporting, and if you click on that, you can go to each and every drug, to see how the committee voted, and weighed in, and discussed, and then it links to each product and all the background materials.

So, if you think about it, we are stepping up the workload. We have tried to move toward a more abbreviated process. So, now that you've heard a long morning of Tamiflu, and then several standard reviews, we are now going to do these, what we're calling, justified abbreviated presentations. So, we've moved to that. We've looked at criteria. There's actually four products that we felt met the special criteria that fall into this category.

So, we want to be taking them one at a time: Taxotere, Omnaris nasal spray, Natazia, and Protonix, and there's the designated abbreviated review, which you will hear tomorrow, which all the criteria pretty much, there's nothing going on. For these four products, we, FDA, in a full review on -- you've got all of the materials in your background, but as we go through, most of the following criteria have been met to fall into this category. So, little, if any use, the drug is not marketed, no deaths, fewer, if any, serious adverse events, no

product safety signal that FDA identified in their review, and the product labeling may have warning black box, et cetera, but we see it as appropriate.

And so then, what I'm going to do is give you the product, give you a little background, and then we are going to provide you with our justification or some rationale why we reached that conclusion, and then we would recommend for all these products, FDA would recommend to return to standard ongoing monitoring. You will have an opportunity to discuss what we would ask you to vote whether or not you would concur, yes or no.

So, we'll start with Taxotere, and I think it's helpful to remember just some important things to keep in mind when you're looking at oncology drugs that there usually is a well known safety profile for the drug product that's used in the adult population, and oncological drug use in children really, in the U.S., it's a small population. Cancers are rare, thank goodness. These products are often associated with significant AEs, but the risk and benefit weigh favor use, particularly in your refractory tumors and children with cancer are going to have higher morbidity and mortality rates that are going to skew the results. So, for this one, Taxotere ended up in this category.

So, a little more about the rationale then. It's

already used for a variety of adult cancers, lung cancer, prostate cancer, stomach cancer, breast cancer, but it was studied, but it is not approved for the pediatric population. The pediatric studies for use with refractory tumors, things like medulla blastoma, leukemia that were studied, demonstrated clinical activity, but the substantial evidence of efficacy was lacking. So, this drug has no pediatric indication. There is little use in the pediatric population, and the use in the pediatric population is limited to the clinical trial setting then, and so those are experts around the country, you know, that follow these patients closely, and also with patients with refractory solid tumors like sarcomas and all, who've exhausted standard treatment options.

Now, when the review was done, and please note, this is, you know, 15 years or so of adverse events, there were a total of 12, two deaths. There was a 9-year-old with T cell leukemia, and he died with what was felt to be presumed fungal pneumonia, a 4-year old with ALL and disease progression, and then the OSE [spelled phonetically] folks looked at everything else, and came up with 10 AEs, including serious and non-serious in this group, and most of the adverse events were expected events with the drug or were felt to be due to disease progression, and there were kind of one or two of each. So, there wasn't a real cluster.

So, with that said, we recommend the ongoing standard monitoring that we do, and would you, the committee, concur?

CHAIRMAN ROSENTHAL: Questions for Dr. Cope regarding Taxotere?

DR. SANTANA: Just a general comment as the hematology oncology representative of the committee, so you're absolutely correct. This drug is not commonly used in pediatric oncology. There is some use in some primary settings, like germ cell tumors, but usually when it's used in a refractory setting, it -- like you said, it's done as a last exhaustion for those patients. So, I think the safety profile that we know about this drug is similar to the safety profile on adults, which infusion [spelled phonetically] reactions and things of that nature. So, I think your assessment is accurate in my view.

CHAIRMAN ROSENTHAL: Okay, thank you for your comment. So, other comments? Okay, let's vote on this. Does the committee concur that FDA should continue its standard ongoing safety monitoring for Taxotere, all in favor? Any opposed? Don't see any abstentions. No, so Dr. Reed, will you just not state your vote?

DR. REED: Michael Reed, I voted yes.

DR. SANTANA: Victor Santana, I voted yes.

DR. RAKOWSKY: Alex Rakowsky, yes.

DR. WAGENER: Jeff Wagener, yes.

DR. TOWBIN: Kenneth Towbin, yes.

DR. JOAD: Jesse Joad, yes.

MS. CELENTO: Amy Celento, yes.

DR. LARUSSA: Philip LaRussa, yes.

DR. GLASIER: Charles Glasier, yes.

DR. MINK: Jon Mink, yes.

DR. WIEFLING: Bridgette Wiefling, yes.

DR. HEWITT: Geri Hewitt, yes.

DR. MOTIL: Kathleen Motil, yes.

DR. WHITE: Michael White, yes.

CHAIRMAN ROSENTHAL: Okay, thank you. Dr. Cope, you can -- so Dr. Ramier can come back to the table for Omnaris, thank you. I'm sorry to do this to you, but it helps with the process, appreciate it. All right, Dr. Cope.

DR. COPE: So the next one, Omnaris, again, we did the full safety review and you all got all the materials in your background package, and just a couple of things on Omnaris nasal spray is approved for seasonal allergic rhinitis in patients 6 years and older, and perennial allergic rhinitis in patients 12 years and older. I also might mention, you'll see the approval dates for those studies in pediatric indications for a few years ago, and actually, Omnaris, in 2009, went as an abbreviated product to the committee. At that time, there were absolutely no adverse events. So, now it's coming back and our

justification is over all the years, an adverse -- including all that, we've only come up with one serious adverse advent that was in the Omnaris database, and it was an in utero exposure. As I recall, it was a baby little heart murmur, and that was what was there. There was no safety signal identified.

There was recent product labeling regarding the post-market studies. It is appropriate for safety FDA summarized. The warning and precautions include information, which was the labeling change about the potential reduction in growth velocity in children, and the need to monitor growth. Just to make an additional note, there is increasing use. So, that was the one criteria that really didn't fit, and we, again, would recommend returned ongoing safety monitoring, and we ask do you consider, do you concur?

CHAIRMAN ROSENTHAL: So, may I ask a quick question before I open the floor for other questions? What is the trouble for bringing this back to the committee, this particular product?

DR. COPE: My understanding, it was the post-market pediatric clinical trials that led to that.

CHAIRMAN ROSENTHAL: Okay. Other questions for Dr. Cope on the topic of Omnaris nasal spray? Okay.

DR. COPE: I actually might just jump in there. It really wasn't that there was a safety signal with that. It was

that the studies that were, I don't know, 52 weeks or whatever, were felt not to be long enough to really follow the growth.

CHAIRMAN ROSENTHAL: Okay. All those in favor of returning this product to routine safety monitoring, please raise your hands. The opposed? Any abstentions? No. Okay, Dr. White.

DR. WHITE: Michael White, yes.

DR. MOTIL: Kathleen Motil, yes.

DR. HEWITT: Geri Hewitt, yes.

DR. WIEFLING: Bridgette Wiefling, yes.

DR. MINK: Jon Mink, yes.

DR. GLASIER: Charles Glasier, yes.

DR. LARUSSA: Phil LaRussa, yes.

DR. RAIMER: Sharon Raimer, yes.

MS. CELENTO: Amy Celento, yes.

DR. JOAD: Jesse Joad, yes.

DR. TOWBIN: Kenneth Towbin, I concur.

DR. WAGENER: Jeff Wagener, yes.

DR. RAKOWSKY: Alex Rakowsky, yes.

DR. SANTANA: Victor Santana, yes.

DR. REED: Michael Reed, yes.

CHAIRMAN ROSENTHAL: Okay, thank you, and Dr. Raimer, we need to ask you to recuse yourself for the next two products that Dr. Cope will discuss. So, Dr. Cope, moving on to the next

--

DR. COPE: Okay, the third product, birth control, Natazia. Again, all of the materials you have in your background, and we gave it a full review, felt that it qualified. It has an improved indication. It's an estrogen, progesterone contraceptive. It kind of goes step down, step down estrogen, and then step up, step up progesterone, used by women to prevent pregnancy, and also more recently, not specifically pediatric, but there was -- it also has an indication for treatment of heavy menstrual bleeding in women without organic pathology, who choose to use an oral contraceptive as their method of contraception.

Justification of this as an abbreviated with safety and efficacy for post-pubertal adolescence under 18 are expected to be the same as those 18 or older, and there is some use in the pediatric populations, but no safety signal was identified, and we thought that the product labeling was appropriate for safety.

When you look at the pediatric focus safety review, notice the timespan is not that long. This is a new approved product. There were six pediatric AERS reports, five serious, four ages 0 to 17. We took it up an extra year because of the way the indication, you know, went under 18, up to the 18th birthday. There were two ectopic pregnancies and one AERS

report each for skin, hepatobiliary, metabolic, and ear/labyrinth reaction, and again, we supported that this should return to standard ongoing safety monitoring and ask you to take a vote.

CHAIRMAN ROSENTHAL: Questions for Dr. Cope regarding Natazia? Yes, Dr. Wagener?

DR. WAGENER: When you say there was some use, do you have numbers on that or would it be possible to just say in the last year there have been X thousand prescriptions, something of that type?

DR. COPE: I don't have the numbers right in front of me --

DR. MEHTA: Yeah, this is Hina Mehta from Drug Use, from May, 2010, through December, 2011, a total of 2,000 prescriptions that were dispensed among patients 0 to 17, there were about 20,000, so, about 9 percent of the prescriptions that were dispensed.

CHAIRMAN ROSENTHAL: Okay, other questions for Dr. Cope? Yes? All right. Yes, Dr. LaRussa.

DR. LARUSSA: I don't know how many patients that represents, but how many ectopic pregnancies would you expect in that sized population?

DR. ROTHSTEIN: This is Adrienne Rothstein, with Division of Pharmacovigilance. We should clarify that she was

providing drug usage in the U.S. This product was approved in Europe and longer than here in the U.S., and of the reports we've reviewed, only one was from the U.S. So, she was providing some data on usage in the U.S.

CHAIRMAN ROSENTHAL: Okay, other questions? Yes, Dr. LaRussa?

DR. LARUSSA: So, I'm assuming you're saying that one out of whatever the population was, there's a reasonable number of ectopic pregnancies to expect?

DR. HAUSMAN: This is Ethan Hausman. We've got one patient that was from U.S. data, that was the weight change. So, the -- okay.

DR. WILLET: For 20,000, that number of ectopics is probably appropriate, because we are going to be picking up Chlamydia in that upper age range.

CHAIRMAN ROSENTHAL: Can you please just introduce yourself to the panel?

DR. WILLET: Jerry Willet, Reproductive.

CHAIRMAN ROSENTHAL: Dr. Towbin?

DR. TOWBIN: Just a comment, it looks like on Page 2 of 12 of the briefing materials, it's 4,400 patients for the 9 percent.

CHAIRMAN ROSENTHAL: Other questions regarding Natazia? All right. Let's everybody express our opinions

regarding whether the FDA should return this product to the standard ongoing safety monitoring. All in favor, please raise your hands. Okay, thank you. Any opposed? Are there any abstentions? Dr. Reed.

DR. REED: Michael Reed, I voted yes.

DR. SANTANA: Victor Santana, I voted yes.

DR. RAKOWSKY: Alex Rakowsky, concur.

DR. WAGENER: Jeff Wagener, yes.

DR. TOWBIN: Kenneth Towbin, I concur.

DR. JOAD: Jesse Joad, yes.

MS. CELENTO: Amy Celento, yes.

DR. LARUSSA: Phil LaRussa, yes.

DR. GLASIER: Charles Glasier, yes.

DR. MINK: Jon Mink, yes.

DR. WIEFLING: Bridgette Wiefling, yes.

DR. HEWITT: Geri Hewitt, yes.

DR. MOTIL: Kathleen Motil, yes.

DR. WHITE: Michael White, yes.

CHAIRMAN ROSENTHAL: Thank you, and now we'll move along to the discussion of Protonix with Dr. Cope.

DR. COPE: Okay, fourth product, Protonix. Just some background, so Protonix is indicated for short term treatment of erosive esophagitis associated with GERD, and is approved for pediatric patients 5 and older, or 5 through 16, in the

pediatric age group, and there is a bit of history on these PPIs. In June, 2010, at the Pediatric Advisory Committee meeting, there were actually four other PPIs that had mandated safety reviews and came before the committee for a long, lengthy discussion, and everyone voiced then, at that point, that there really was need for additional data on use and safety in the pediatric population. Then, just a couple of months later, FDA had a joint AC, so it was the gastrointestinal group and a few from the Pediatric Advisory Committee, and I think it was risk mitigation, and they really talked about how PPI use as being used for GERD in infants, and younger children, and the recommendations from that meeting included further pediatric studies to assess PK safety and use, with appropriate study end points.

Also, FDA took efforts thereafter to start an ongoing pilot study to see if we could get more data on the use and safety profile of PPIs in hospitalized patients, and actually, Dr. McMahon is going to talk about that after this product review.

So, there are a couple of other things that I just wanted to mention about Protonix. Actually, first of all, if you look in your review, there is tablet suspension and intravenous forms. The intravenous form is not approved for children. So, we'll get to that in a minute, but early this

year, PPI labels for some of the other PPIs included information in the warning, precaution section, about concomitant use with Methotrexate, specifically mentioning Nexium, but they talked about problems with it being used with Methotrexate, that it might elevate prolonged serum levels of Methotrexate, and/or its metabolites, and possibly leading to Methotrexate toxicity, and the point for Protonix is that is that is now, you know, often we'll start with a couple of drugs and lead up to the whole class. So, it was early February, 2012 that FDA, the division requested that the sponsor make the same labeling change for Protonix as well, i.e., in oral formulations, suspension, and tablets.

The other thing that came out, I don't know if you caught this, but also in February, there was a drug safety communication about, they call CDAT, clostridium difficile associated diarrhea with use of PPIs. I'd like to make an important point that we triple checked. There are no pediatric AERS reports for C difficile that FDA has received. And I think if you go to the website link, that you would see, I think the biggest concern at this point was that it was used in people who are already on antibiotics for a long time, elderly, and more chronic diseases, but I just want to mention that as well.

So, with justification of the abbreviated, first of all, there is a considerable use in the pediatric population.

Also, I mentioned to you all the meetings, and all the reviews, and all that we've done in the last couple of years, and that we're looking at these issues, and so this pediatric safety review went from the ones that had gone before. There were zero deaths and five serious AEs between March, 2010 and December of 2011. There were three AERS reports with the oral formulation. So remember, the IV is off label, but we looked at all four formulations, and there was a 15 year old with anaphylaxis. There was a 9-month-old with a feeding tube complication, which was an unlabeled event and an off label use. It's not to be used in that young age group and with that feeding tube that was used, and then there was a 13-year-old who was medium depressed.

There were two AERS reports using the intravascular formulation off label, and it was a 3-year-old with hypertriglyceridemia, and a 10-year-old with ALL, who as I sort of mentioned before about the Methotrexate, as it turns out, had decreased Methotrexate clearance while receiving the Protonix. So, that's a little more complicated, but we really felt that it could go justified abbreviated, and we recommend that it continue its standard ongoing safety monitoring, and ask that you vote.

CHAIRMAN ROSENTHAL: Questions for Dr. Cope? Dr. Motil.

DR. MOTIL: I'm sorry if I missed it, but you

specified the use in children, in your presentation, the volume of use?

DR. COPE: Yeah, that it is used somewhat. Maybe you -- I don't know, do you want specific figures?

DR. MOTIL: Well, I was thinking about it in relative terms to Nexium versus Anseprazole [spelled phonetically], the supplement, Lansoprazole and Eprazole [spelled phonetically], all these other drugs were not approved for IV use and Protonix was the first PPI really that was approved for intravenous use, and so it was certainly used in the hospital setting.

DR. COPE: Yes, that's one of the reasons we looked at intravenous use and we went back a ways, and that was covered in some of the other PPI meetings as well.

DR. MOTIL: I didn't remember discussing it, but if we did, okay. Do you have some use [unintelligible] group?

DR. COPE: Yeah, we still have more slides, because it was abbreviated.

FEMALE SPEAKER: It's in the background package. For the number of patients in the hospital setting, for the injectable from the year -- December, 2010, through November, 2011, a total of 7 million patients had a hospital billing for Protonix, patients aged zero to 16 were 35,000, of the injectable was 3.4 million patients had their hospital discharge billing for Protonix. For the oral, there were about 4.1

million outpatients. Patients age zero to 16 were at 13,000.

CHAIRMAN ROSENTHAL: Thank you. Other questions regarding Protonix? All in favor of continuing current ongoing monitoring, safety monitoring for this agent, please raise your hands. Thank you. Any opposed? I see none. Any abstentions. I see none. Dr. White.

DR. WHITE: I voted yes, Michael White.

DR. MOTIL: Kathleen Motil, yes.

DR. HEWITT: Geri Hewitt, yes.

DR. WIEFLING: Bridgette Wiefling, yes.

DR. MINK: Jon Mink, yes.

DR. GLASIER: Charles Glasier, yes.

DR. LARUSSA: Philip LaRussa, yes.

MS. CELENTO: Amy Celento, yes.

DR. JOAD: Jesse Joad, yes.

DR. TOWBIN: Kenneth Towbin, I concur.

DR. WAGENER: Jeff Wagener, yes.

DR. RAKOWSKY: Alex Rakowsky, yes.

DR. SANTANA: Victor Santana, yes.

DR. REED: Michael Reed, yes.

CHAIRMAN ROSENTHAL: All right. Dr. Raimer, if I could ask you to rejoin the -- pardon?

INFORMATIONAL UPDATE:

PRELIMINARY DATA FROM A PILOT STUDY OF SCIENCE AND DIRECTOR OF PROTON PUMP INHIBITOR USE IN INFANTS <1 YEAR IN INTENSIVE CARE UNITS

CHAIRMAN ROSENTHAL: Our next speaker, continuing on a theme of PPIs, our next speaker will be Dr. Ann McMahon. Dr. McMahon received a Master of Science in health policy management from Harvard School of Public Health, from which she went on to receive a medical degree from Case Western Reserve University. She completed her residency in pediatrics at Johns Hopkins, and continued with post-doctoral training at National Institutes of Health, in Johns Hopkins, in virology and pediatric infectious diseases. After an assistant professorship at the University of Chicago, she saw the light and she joined the FDA in 2002 -- I'm embellishing a little.

Since joining the FDA, she has focused on post-marketing safety, the first five years primarily on vaccine safety in the Center for Biologics Evaluation and Research, and the last five years primarily on the safety of drugs and biologics, in the Center for Drug Evaluation and Research.

She currently holds the title of Associate Director of Science and Director of KidNet, in the Office of Pediatric Therapeutics, in the Office of the Commissioner.

And Dr. McMahon, I just want to recognize that you have been a pillar of the activity of this committee for all the time that I've been on it, and it's been our pleasure to work with you in this context.

DR. MCMAHON: Thank you very much for your kind introduction and I know that I have the unique position here of the last talk of the day, so I'm going to try to be short, funny, or probably knowing me, I think short might be something to aim for a little bit more so than funny, but -- so I'm going to try to stick to that.

This talk is a brief update on the pilot project on proton pump inhibitor use in infants, and in this case, I'm referring to infants as less than one year of age. This project was requested by the Pediatric Advisory Committee several years ago. There are two objectives in the overall pilot project, one, to determine off-label medical product use patterns in children, and two, to explore an alternative mechanism for safety assessment of products being used off label in children.

I want to do something a little bit different than is often done at the advisory committees, and show you the question upfront. Okay? So, this is the question that I'm going to be asking you at the end of the talk, this brief talk, and I want you to be thinking about this as I go along. Does the committee have suggestions for further areas of study using this mechanism

that I'll be describing?

Drug use data in particular are limited in children less than 1 year of age. This pilot study used an existing FDA surveillance system known as MedSun. The objects of PPI study are to determine the patterns of one, drug use, and two, adverse events in infants treated with proton pump inhibitors.

This slide describes the current status of the PPI pilot project. A contractor extracted data from two complete sites and one partial site. A physician also extracted data from the partial site, and we "deduplicated" the data from the contractor physician pair as best as possible. So, then put the data all together into one pot from all the sites.

There is one site that still has data to come in. So, in this pot from all the different sites, there were 83 patients represented, after deduplication. There was a mix of ancestries among these preliminary -- the data that we got from the preliminary patients; the majority were African American. Okay.

In this preliminary dataset, the vast majority of the patients were from the NICU, and a smaller number were from the PICU, or other ICUs, primarily pediatric coronary intensive care units. In this group of other there are the EC [spelled phonetically].

You will see this type of box plot in a number of times in the talk. The plot shows the median. Let's see if I

can get this going here. I think I have it. Oops, nope, wrong. Okay. Sorry, can't do it. Okay, let me do it this way. The median is shown here and the maximum, and minimum. Okay. Okay, thank you. I think we're back on step here. So in this case, there was a tremendous range of birth rate with a maximum near 6 kilograms, and a minimum near zero kilograms.

Note in these preliminary data that the vast majority of babies studied received Prevacid and this either -- this, they received either orally or entirely. Those who received Protonix received it intravenously. Notice on this box plot that there are several filled in dots above the plot. These are observations that are out-wires. In this case, the mean age when treatment was started with proton pump inhibitors, was about 10 weeks, and the mean length of stay in the pilot study was 47.51 days. The mean number of days of PPI administration, with an N of 80, was 15 days.

One might wonder whether the number of days the drug was administered tracked with length of stay, which might itself track with ICU sites. So we looked at this, chart shows days on the Y axis. The number N is considered each sample shown above each column, and the blue bars represent mean length of stay. The red bars represent the mean length of treatment. So, there are -- in this sample, the length of stay varied substantially by ICU site. Duration of treatment did not vary by ICU site.

Of course, one of our major interests was the indication for which this off-label use was occurring. Unfortunately, only 22 questionnaires out of 83 designated the reason that the drug was being given; 20 out of 22 designated GERD, or gastroesophageal reflux disease, and note that some of the missing data may be due to varied data collection procedures. So we had some sense that in some sites, we may have gotten more of the data on indication than in other sites.

The mean dose in milligrams per kilogram per day was 1.5, and generally, you give daily dose in milligrams per kilograms, 1 to 2. The generally recommended dose in older children on PPI labels is less than or equal to one milligram per kilogram, per day.

Most frequently used daily dosing in this sample was once per day, but a number of entrance were administered PPIs twice daily. The dosing recommendation, by the way, in older children on the label is once daily.

This slide shows the adverse events extracted from the charts in more than one patient. So, it really does the onesies, or the ones that were just one per patient. Okay? There were 118 adverse advents seen in more than one person. More than one of these may have occurred in a single individual; therefore, these counts represent adverse events, not individuals.

Of the 118 adverse events, 34 percent were respiratory and 20 percent were cardiovascular. Of these, a good number were preexisting conditions; therefore, my assessment is that the high incidents of, well, proportion of respiratory and cardiovascular events has to do with underlying morbidity of the patients, and probably less so to do with the drug. The remainder of the events were scattered in a number of systems, and again, many of them were preexisting conditions.

From two sites which we received denominators of less than 1-year-olds admitted to relevant ICUs, we found that in those two sites, 3 to 5 percent of babies less than one year of age would be administered PPIs.

So overall, I wanted to just go through what we consider some of the limitations of this small study. First of all is that it's small. Many exclusions for serious illnesses, age, timing of admission, et cetera, made the studies quite small, in addition to the fact that we were starting with a small number of sites. One hospital hasn't yet provided data, so we'll have a little more data as we go along. Some duplication in patients may have occurred, although we did make every effort to weed out the duplicates.

Variability in extraction methods may have occurred and reliability of data entry that was not perfect. There was -- we measured it and it was 2 to 4 percent error rate. And, of

course, we didn't have a comparison group, and we didn't have any randomization. So it's difficult to assess adverse events, and their significance.

So the conclusions that we felt we could draw from these data are that 3 to 5 percent of the infants less than one year of age were receiving PPIs in the sample in the intensive care units. That admission to NICU versus PICU does not appear to predict length of treatment with PPIs, despite potentially having differences in length of stay, depending on the NICU versus PICU.

The dose administered in this setting was generally 1 to 2 milligrams per kilogram, per day. Twice the number of patients received PPI on a daily fashion, compared to twice daily. To date, there is no obvious PPI related safety signal in these infants using PPIs off label, and further data from this study will provide additional preliminary information, which might inform future controlled studies.

And so here's my question to you, and -- but I do say that I'd be happy to take any questions about what I just said, at any point. I don't know how Dr. Rosenthal wants to handle that, but --

CHAIRMAN ROSENTHAL: Yes, Dr. Goldstein with a question or comment?

DR. GOLDSTEIN: My comment is that when you're

catching adverse events, to me, it doesn’t make any sense. I belief that if you have a preexisting condition, an adverse -- I may be wrong, an adverse event needs to be either a worsening in the severity or the frequency of that preexisting condition. So to list Down syndrome or double [unintelligible] as an adverse event is erroneous and misleading. Again, I may be mistaken, but I don’t think so.

DR. MCMAHON: Shall I respond to that? Yeah. Yeah, I mean I completely agree with you. I mean, I think what I did was to put down the data on paper that I had, and this was extracted from the charts by a whole variety of different people, and a lot of it isn’t directly relevant to the question at hand.

DR. GOLDSTEIN: How'd you -- I mean I applaud the evidence, but I would like you not to put down irrelevant, or inaccurate data, there's -- it takes on a life of its own.

CHAIRMAN ROSENTHAL: To begin, the purpose of this presentation is just to circle back to the Pediatric Advisory Committee.

DR. GOLDSTEIN: I understand, but if they don’t capture the data correctly, we won’t be able to assess the adverse events when the study is -- completely agree.

DR. MCMAHON: Right. Did you have something --

DR. GOLDSTEIN: Oh yes. I haven’t seen the

questionnaire, but I -- maybe I missed it, but I didn't see anything about -- is there in the questionnaire about changes in symptomatology, which to me would be the reason that you would want to, other than dosing, would --

DR. MCMAHON: You mean the efficacy?

DR. GOLDSTEIN: Yes.

DR. MCMAHON: Yes -- no. It's not in the questionnaire, but I did notice it. As one of the chart extractors, I saw comments about it in the charts, so --

DR. GOLDSTEIN: If you want to do something about pharmacodynamics, it would say population in this drug. To me, it would seem like this would be an important --

DR. MCMAHON: Well, the whole question -- I think the whole question of using this mechanism for efficacy is one that Dr. Murphy might want to comment on.

DR. MURPHY: It's not set up for that, first of all, and secondly is I think what this pilot showed us is that trying to get at even anything beyond use data is going to be very difficult, because what we found is a couple of things, and we could spend a whole discussion on this, but is that just trying to get the indication was amazingly difficult. You wouldn't think it would be, but getting the indication for why the child was put on the PPI was not as clear as you would have thought it would be, and then we did have, you know, boxes that said,

basically, after this child was put on this indication, did you have any of these symptoms. We didn't even ask them to make attributions into the symptoms, and it doesn’t -- it’s just very difficult because these kids have all these things, and if you saw, people end up giving us things that obviously are not adverse events. And so I think --

DR. GOLDSTEIN: Are those PICU med [spelled phonetically] sites or Vermont Oxford Network sites?

DR. MURPHY: These were basically sites that are in the MedSun units, and they --

DR. GOLDSTEIN: I’m sorry, I don't know what that is.

DR. MCMAHON: But they were NICU, PICU, and SICU of various hospitals.

DR. GOLDSTEIN: But if they weren’t research sites, you know -- quite know how to do this, then that's an issue as well. I'm sorry, I'll --

DR. MURPHY: We have some very high caliber hospitals in this, okay? I mean that’s -- it’s very difficult to go in retrospectively and try to find this information, and all I can say is that electronic documents are not helping either. I mean people had to go and pull written charts. That’s what Ann McMahon has been doing, and because the contractor, it was a bust. I'm just being very blunt with the committee; it's late in the day, and I'll spare words.

You know, basically she'll go back and redo it, because you need either a neonatal intensivist [spelled phonetically], or you need a nurse who will work the neonatal intensive care unit to go in and look at these really complicated charts, to try to figure out what's going on. So, I think what we're finding is for --

CHAIRMAN ROSENTHAL: Hang on just a sec. Dr. Goldstein, you can't drop the grenade on the committee and then walk out of the room. Okay, but I think we get your point that this is a tough process. Hang on. We've actually got a list of questions. It's about six deep right now, so Dr. Hudak is next.

DR. HUDAK: Well, I certainly will concur. It's very difficult to figure out sometimes why this drug in particular is used. So, there are 83 cases. We've had 22 reasons why the drug was -- is provided. So, let me give you my insight into this. So with NICU, what happens is this is a drug that is used for babies who may have residuals. Just because people think that it will help decrease residuals, makes no sense, but that's what happens, and it's not written down on the chart anywhere, or a kid may have some bicardials [spelled phonetically] or whatever, or may have some split-up, or whatever, and it's used; it's not very good, but it's sort of what happens with NICU. In the PICU, on the other hand, with the very sick kids who are NPO for several periods of time. It's sort of a routine to just

prescribe -- it used to be, you know, cymidadine [spelled phonetically], you know. Now it’s proton pump inhibitors to reduce acid in the stomach because their NPO and the thought is you are prophylaxing against, you know, ulcer disease and so forth, and so on. So, there's not a reason to chart -- it's something that gets started on rounds because we decided we’d have our PPI, you know, on bordiac [spelled phonetically] this kid's been on NPO for two days. The kids on ECMO and is not being fed, and so that’s just part of the protocol; it's not written in the chart anywhere to find a reason.

CHAIRMAN ROSENTHAL: Next is Dr. LaRussa, and then Dr. Mink.

DR. LARUSSA: So Ann, maybe this is not a useful suggestion, but I think trying to do this retrospectively is not going to work and you may want to consider doing it prospectively.

CHAIRMAN ROSENTHAL: Dr. Mink.

DR. WHITE: I was indentified earlier.

CHAIRMAN ROSENTHAL: Okay, sorry. So, Dr. White.

DR. WHITE: We’re having to make a transition to using one of the major electronic medical records. It seems to me you would benefit by getting in touch with the major manufacturers or developers, and find out what it takes to get incorporated into their system, the means of getting through why a

prescription is written. We have to put in an indication before we can enter the prescription into the database, and we do, we do. That's what they tell us. We'll find out, but you should -- why even struggle with paper, because it's -- we're going to burn all the paper soon. It's going to go away, but we have a slog problem on the East Coast, but we're going to burn all the paper.

So if you could get in touch with the developers now, before they're putting all these things in place, and make it absolutely mandatory that, hey, we need this data, so you're going to put it so that we have to enter an indication when we start a medication. That will give you access and I think it can be done, but you have to hurry before everybody adopts these things.

DR. MURPHY: I mean I agree, it would be great. The thought that we would have any influence on this is [laughs] just to bring in all these guys, to see if we could even get coding coding for safety--

DR. WHITE: But you do have the influence because the government's paying for most of these, and I mean there's this need for use criteria, and if you don't meet that, then you don't get the money.

DR. MURPHY: We don't even have pediatric codes, okay?

DR. WHITE: I agree with that, yeah that's --

CHAIRMAN ROSENTHAL: And so, this is going to be --

DR. WHITE: Like the patient with the heart murmur that got bigger.

CHAIRMAN ROSENTHAL: We could continue to discuss this, but I'm going to ask that the temperature be turned up in the room, if you guys continue to -- so, Dr. -- you get my point. So, Dr. Raimer, and Dr. Motil, and then Dr. LaRussa, and then those are the questions that I've got written down.

DR. WHITE: So, I was just going to make a suggestion for the future. So, one was what actually came up earlier, and that is that some of the use is being driven by protocol, and so which ever place you go, I would ask them upfront, you know, we're studying this -- we want to look at this trial, but do you have any protocols that include this in therapy. So, that will get rid of a lot of the cases, and in ICUs in particular, if that's the case.

The second is the electronic medical record will not be the solution. When you're putting these --

CHAIRMAN ROSENTHAL: Can you turn up the temperature, please. Just go up all the way, as high as it gets. It's just like --

DR. WHITE: When you're putting the medications, if their system asks you to tell why, the doctor will simply push a button that says associate all, and that makes the diagnosis go

into every drug that's there, and it is garbage in, garbage out.

CHAIRMAN ROSENTHAL: Dr. Motil.

DR. MOTIL: Well, first of all, I guess I would say that it is true that the electronic medical records are useless because they -- even though they ask you to write the prescription, that specific drug was not to what you wrote in for the diagnosis. That does not have to happen even in epic -- the biggest system. So, it mixes up all sorts of stuff and you can hit it until you are blue in the face. You cannot get the indication to match the drug, and to save time for which we don't have, and just ignore it, and push the button. You're correct. So I would not use that. What I would use for a systematic approach would be to hire someone who is committed to tweaking the data for every bloody question you want answered, and that would be the best at interest of a single person, or people, who are engaged in the project.

CHAIRMAN ROSENTHAL: Dr. LaRussa.

DR. MOTIL: Wait, wait. I'm not done. I'm not done. I have some more suggestions.

CHAIRMAN ROSENTHAL: Turn off the fan, please; the air movement in here is just too much, when it's still and hot.

DR. MOTIL: Number two, for those of us who prescribe this stuff because it's our trade, we do have reasons for using those particular drugs. I would suggest that if it isn't

written down, it's partly laziness, and partly just passing over, not writing an indication down, but we do.

Most of the time it’s related to -- well I'll come back to that in a minute -- because a third thing is I think you’re talking about apples and oranges if you do the NICU versus the PICU. Those are two different settings, and so you have to refer to the question a bit more to what do you really want to study, which group. I was surprised that you had the NICUs in because their symptoms are going to be different than PICU.

And so coming back to this, what are the indications in NICU? The symptoms that you wrote down, the respiratory stuff, well, most of the time, these are babies who have apnea or bradycardia, and so you evaluate them for the reflux issue, and the assumption is because you can’t always temporally correlate apnea and reflux, you assume that’s it’s there. You can find no other explanation, you start the PPI as a prophylactic measure to mimimize ongoing respiratory difficulty. You might prohibit -- you capture these events dogmatically with the PH pro, for example, it's slim to none, bu you can do it. And in a PICU, it is true that for those of us who have endoscope bleeders [spelled phonetically] and set up a sterile worksite for the endoscoping, you would rather prevent that kind of encounter if it’s going to occur. So the PPI has become

protocol. It may not be stated in the PICUs, but for those of us who see the bad consequences, it's the same thing with [unintelligible]. I never want to see a kid coming in DOA and have short term memory loss, if I had [unintelligible] symptomatic or not, I treat because I see all the bad stuff coming in. And I prophylactically want to prevent those bad outcomes.

CHAIRMAN ROSENTHAL: Thank you.

DR. MOTIL: One other thing --

CHAIRMAN ROSENTHAL: Hang on, let me just say. When they give you the chair job around here they tell you that you can turn off people's microphones, if you need to. I've never done it. Go ahead, last point.

DR. MOTIL: Last point, you might want to, if you want data to assess, you might measure volume of formula administration in conjunction with PPI use, because then if you're looking at regurgitation vomiting issues because of reflux the more volume you feed the baby with the way we may see symptoms. That's all.

CHAIRMAN ROSENTHAL: Thank you, Dr. LaRussa.

DR. LARUSSA: My comments were covered.

CHAIRMAN ROSENTHAL: Thank you. So, I think, you know, Dr. McMahon asked us a pretty straightforward question, which I don't think we answered, unless the answer is just no.

The answer is no. Dr. Wagener?

DR. WAGENER: So, to address that question, does the committee have suggestions for further areas of study? I would say there are maybe two questions, the first question is, is this drug used in the nursery, PICU, CICU, whatever. If, indeed, we are asking that question, that should be able to be answered electronically, you know, tie in, basically, date that the prescription started with how many kids are in the unit. So, that’s a super electronic question. The second would be why do we want that information, and if we want that information because we are worried about adverse events then we're going to have to do with prospective study and you're going to have to collect data from the beginning. So, two questions, two approaches.

ADJOURNMENT

CHAIRMAN ROSENTHAL: Thank you. If we can just keep talking for a little while longer, we can start tomorrow morning's meeting without ever going home. I'm kidding. Thank you all for your discussion. If there aren't other points, we'll adjourn the meeting today. I'll ask the people please do not talk about this -- don't continue this discussion away from the table, or please don't discuss other things that have come up in this meeting, or will be discussed tomorrow.

The meeting tomorrow starts at 8:30. The agency is giving us a little bit of a break and I want to thank everybody for their participation in the discussions today. Thank you.

(Whereupon, at 5:46 p.m., the meeting was adjourned.)

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